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RESEARCH INTO THE FORMATION OF AUTOSYNTHETIC CELLS

WITH SPECIAL REFERENCE TO FERTILIZATION, THE PRODUCTION & GROWTH OF CANCER CELLS & THE CAUSE OF FATTY DEGENERATION*

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IT is my first and most pleasant duty to put in words my sense of appreciation of your invitation to me to deliver the William Potter Memorial Lecture. My regard for Chevalier Jackson is so great that his invitation was my command.

The research here presented, was carried out in the laboratories of the Cleveland Clinic Foundation, in collaboration with Maria Telkes, PH.D. and Amy F. Rowland, M.A. I wish also to make acknowledgment of the advice and assistance received from Professor Dayton C. Miller and Professor W. R. Veazey, of the Case School of Applied Science.

There is much evidence that cancer cells vary greatly in their activity, in comparison with the cells of the host.

1. Cancer cells show a change in nucleus plasma relation, as compared with the host.

2. The conductivity and capacity, in actively growing cancer are higher than in the host.

3. Opinions differ widely, as to the rate of metabolism in cancer, as compared with that in the host.

4. Many cancers and tumors are more sensitive to radiation than the host.

5. Cytologists, notably Broders, have been able to some extent to base a prognosis on the degree of differentiation of the cancer cell.

An interpretation of the conductivity and capacity of cancer tissue, as compared with the host, must be made tentatively, since in the cancer mass there is a greater preponderance of cells and this in itself would increase the conductivity and the capacity. The only safe comparison would be the measurement of the conductivity and capacity and metabolism of a single cell.

At this time we propose to consider the facts that would be harmonized by the conception that cancer cells are reduced normal cells, that their success in growth is due to the fact that the cells of the host are differentiated, that their energy is spent within the cell in function while the cancer cell having no inner function expends its energy in growth only.

The cancer cell, like the cell of the host, is made up of proteins, lipoids and electrolytes, the chief difference between a cancer cell and the corresponding normal cell being that the energy of the normal cell is used principally in the performance of the specific work for which the cell was differentiated, while the cancer cell uses its energy principally for growth, and little or not at all for function.

Between the normal cell that may grow and the cancer cell that may perform some specific function, there is a vague zone of identity.

* The William Potter Memorial Lecture, 1931, Jefferson Medical College, Philadelphia.

Within this zone in certain cases the cancer cell may even perform a specific function identical with that performed by the host. Thus, as Wells states, even "metastatic growths of thyroid tissue, will produce thyroidin in any part of the body; liver carcinoma metastases produce bile; tumors from the choroid or from pigmented moles produce melanin." In certain cases, malignant cells bear certain chemical characteristics of the parent tissue, as in the case of the high content and quality of the lipoids in hypernephroma, and the content of iodine in cancer of the thyroid, while over-function of malignant tissue is seen in melanoma of the skin (Ewing).

Like normal cells, cancer cells are killed by radiation and by loss of their blood supply; they grow slowly in old age; they are stimulated by irritation; they become infected; they undergo fatty degeneration; they take vital stains in some relation to their rate of growth and activity; and they show changes in electric conductivity, capacity, and potential, in relation to changes in their growth or functional energy. Like normal cells, cancer cells show a relation between rapidity of growth and degree of differentiation. The more differentiated the tissue, the less energy is left for growth, while the most highly specialized cells, the brain cells, have completely lost the power of growth. In normal tissue, the opposite extreme is seen in the contrast between embryonic and adult tissues. The energy of a fertilized ovum is as completely used in cell division as that of cancer cells in growth. As differentiation progresses and tissues and organs form, there is a gradual increase in the use of the energy of the cells for the performance of function; in other words, as function increases, growth diminishes. And finally, function and maintenance of structure use up so much of the energy of the cell that none is left for growth: the adult status is attained. It is obvious that cancer cannot develop in early fetal life, for fetal growth-energy is more vigorous than cancer growth-energy. Such is the relation between the pure cancer cell, whose principal or only use of energy is growth, and the partially differentiated cells in benign tumors: that is, in benign tumors and cancer and under normal conditions an identical principle of energy transformation is manifested. A cancer cell, therefore, is probably a normal cell in which that part of its structure which used its energy for its particular function has been transformed into a structure which uses its energy for growth, and once capacity for growth has been established in a cell, at the expense of function, that cell would be expected to continue to grow and to multiply at the expense of its neighbors having lower growth-energy.

It is important to note that without physical, chemical, or radiation injury, the energy of no normal cell is transformed from the higher form used for function into the lower form used exclusively for growth. Thus, an ameba could not have a cancer; it already has continued growth-energy.

Physical, chemical, and radiation influences have great power of modifying both function and form of cells. This fact brings us squarely to the crux of our problem, namely, how can we divest differentiated cells of the side chains of the molecules of their lipoids and proteins which evolution has added to the simple undifferentiated cell, thus converting the simple growing cell into a cell with some other function.

If there were some way by which we could take from normal cells the fractions necessary for growth and leave behind the fractions for function, we would advance a long step toward the solution of the problem.

In Nature we have well established examples of cells that exist for a time for growth only. In the case of the sex cells, the energy, after fertilization has been effected, is transformed at first into growth-energy alone. The ameba divides into two identical amebae, each going its

own way. If the millions of cells of the rabbit should, like the ameba, divide at the same moment, there would be, as in the case of the ameba, two rabbits, but inseparable. This dilemma in higher animals has been overcome by assembling two essential fractions, bearing opposite signs of charge (as stated by Keller), that have been kept separate from each other until the biologic moment for the formation of a new animal arrives. On the bringing together of these fractions in the sex cells of animals bearing opposite signs of charge, a vigorous coalescence takes place. The sex cells which, according to Keller, bear opposite signs of charge, like all living cells, contain three essential constituents, electrolytes, proteins, and lipoids. The sex elements bearing the formula of their complicated parental protein and lipoid molecules, develop into functional differentiation. Growth wanes as differentiation proceeds. An embryo could have no cancer, for, as stated, all the cells of the embryo have a vigorous growth energy, greater than that of cancer cells. Theoretically, embryo cells would eat the cancer cells; they would become the "cancer" of the cancer cells, as the result of successful competition with the cancer cells for energy. As the embryo man develops as a fetus, as an infant, as a child, a gradually increasing proportion of the total energy is taken by function; while growth, by so much, is slowed down. With this gradual transference of energy into function and withdrawal from growth, the chances for pathologic growth increase. That a tumor or cancer cell is not as vigorous as the embryonal growing cells of the organism is seen by a comparison of certain physical constants, such as conductivity, capacity, and potential; by metabolic rates; by the organizing power of the lipoids of fetal tissue, as contrasted with the organizing power of the lipoids of cancer; and by contrasting the iodine number of the lipoids of fetal tissue with the iodine number of the lipoids of cancer. On the basis then of such a conception of the relation of energy of the tissue to cancer growth, one would not expect to find cancer in the fetus with its high growth energy; nor would one expect to find cancer in those adult tissues and organs having a high metabolic rate, such as muscle, grey matter of the brain, and the adrenal cortex. On the other hand, one would expect cancer to appear commonly in tissue of low metabolic rate, such as epithelial tissue, connective tissue, bone, and lymph glands.

Many observers, notably Cohnheim, have discussed the resemblance between the growth of a fertilized ovum and the growth of a cancer cell. Klefs proposed the hypothesis that a cancer cell is the result of "fertilization" of a normal cell by a leucocyte. Now since in the growth of a cancer cell there admittedly is an analogy to fertilization, my associates and I approached the problem from another angle, namely, we proposed to reduce normal cells from the more complicated molecular structure required for function to the simpler molecular structure required for growth; in other words, we proposed to reduce the adult cell whose energy is used for function toward the simpler embryonic type in which the energy of the cell is used for growth only.

In the entire organism there is normally not a single cell endowed with no purpose or function; in other words, normally there is no cell endowed with growth-energy alone. The overwhelming experience of the clinic has been expressed no better than by the statement of Billroth that "Cancer never appears spontaneously in uninjured tissue." This is also the general conclusion of students of cancer.

We may safely start then with the premise now widely held, that cancer cells are normal cells so structurally altered by mechanical, chemical, or radiant energy that they are partially or wholly bereft of their power of transforming energy into function, but have not lost the power of transforming energy into growth; in other words, a cancer cell is a reduced normal

cell existing at a level above fatty degeneration and death: a cancer cell is an injured normal cell. As stated, this conception is most commonly accepted by students of the cancer problem.

As we have stated, there are three fractions of cells, each of which is essential to their formation, growth, and function. These fractions are electrolytes, lipoids, and proteins. The sex cells carry these three fractions so completely that growth and differentiation are carried to completion in the image of the parents.

In the laboratory, it is obvious that such a faithful reproduction cannot be achieved, as the delicately poised side chains making up the half living lipoid molecule, and the delicately poised fractions of the chemically versatile protein molecules could not be separated without depriving the cell of the power of performing its specific function. Nevertheless, if we were to choose an organ whose structure and function are on such a high level that although the great lipoid protein molecules would support the loss of many side chains, there would still be left enough of the lipoid and the protein structures to form a lower form of cell, we would choose the brain. The brain has the largest proportion and the highest order of the lipoids which, as contrasted with the proteins, have in themselves the power of oxidation and which also bear within themselves structures that may well be the forerunners of cells, e.g., negative glycerol and choline, and positive fatty acids held in the fields of phosphorus and potassium. The brain lipoids and the proteins from the brain or any other organ together with electrolytes, when mixed together should unite vigorously, for the lipoid and the protein bear opposite signs of charge as do sex cells, and these should unite to form a low or reduced order of cell which would exhibit the fundamental characteristics of living protoplasm, viz., irritability, reproduction, and respiration.

Many attempts have been made to produce artificial cells. Such phenomena as division, growth, ameboid movement, and other phenomena have been observed and described by many investigators, notably Bastian, Beutner, Butschli, Herrera, LeDuc, Lehmann, J. Loeb, MacDougal; but despite the painstaking efforts, supported by profound knowledge and brilliant technique, no artificial cell hitherto reported has had the power of energy transformation, the most fundamental characteristic of a living cell.

The artificial cells produced by these investigators may show a nucleus and inner organization, they may divide, show ameboid movement, and superficially, they may resemble living cells, but they cannot of themselves transform energy. The nearest approach to normal cells seems to be those cells constructed by MacDougal, in which a difference in potential was maintained on the opposite sides of the membrane.

The extent to which our expectations regarding the formation and function of such autosynthesized cells have been realized, is summarized in the following brief report of experiments performed in collaboration with Maria Telkes, PH.D. and Amy F. Rowland, M.A.

From the organs of freshly killed normal animals, the lipoids and proteins of the brain were extracted and the ash obtained. By mixing together the brain lipoids, the brain proteins, and a solution of the brain ash, or of the electrolytes contained in the brain, the process of fertilization in Nature by the uniting of the spermatozoön and the ovum was crudely imitated.

On observation of this mixture of brain lipoid, brain protein, and solution of electrolytes under the microscope, we noted immediate activity of organization. Cell-like forms appeared and grew slowly. They multiplied, sometimes by budding, and sometimes by direct division. These cells were nucleated; they took vital stains; they consumed oxygen; they gave off carbon dioxide and they produced urea. Under a high magnification, free movement

of granules and a movement, not unlike the Brownian movement, was seen. Their activity was increased by electric stimulation. Some of these have continued as active cells, for four months.

Exactly the same technique was carried out for the other organs of animals. The lipoids and proteins of the various organs other than the brain were extracted and the ash obtained, but upon mixing the lipoids, proteins, and a solution of the ash of these various organs, only feeble or no power of organization, was seen.

We next observed the effects of adding the brain lipoids to the proteins and solutions of the ash of each of the other organs. Immediate organization was observed. The cell-like structures that were formed took vital stains; they grew in size; they multiplied and they showed respiration.

This experiment revealed clearly that the brain lipoid is unique in being the possessor of a structure that in collaboration with the electrolytes has the power of organizing the proteins of any organ.

As we have stated, these autosynthetic cells showed vital stainability. They grew and multiplied. They showed internal organization such as a nucleus, granules, etc. They varied considerably in size. They had respiration, their oxygen consumption running as high as 14 cu. mm. per hour per 2 c.c. of cell mixture, over a period of five hours, the respiratory quotient for this period ranging from 0.7 under normal conditions, to 0.98 when glucose was added. Some of these cells were observed for a period of nine hours and many photographs, showing the changes in their form, were taken. The form of the cells seemed to depend on the pH of the electrolyte solution, ciliated cells being always produced in a solution of pH 7.5.

While we were carrying out the effects of adding various "food" substances to the cells, it was found that glucose increased the metabolism of the cells, while the various culture materials, such as beef broth, agar, blood serum, etc., showed little or no effect. It is necessary, however, in order to keep cultures "alive" over a period of time, to "feed them" by the occasional addition of protein. When adrenal protein was added the cell immediately assumed the appearance of an ameba and pseudopodia, like those of an active ameba, were thrust out. The usual manner of movement was by the thrusting out of a loop of fiber-like substance from the body of the organism, into which loop the contents of the organism, the granules, etc., seemed to flow, the organism moving in the direction of the flow.

Of special significance was our finding that autosynthetic cells were not formed in the brain-lipoid-brain-protein-electrolyte mixture of dogs which had died from distemper. Of singular significance is the observation that in rabbits which had died of exhaustion from insomnia, the power of cell formation was lost.

On the addition to the brain lipoids and proteins of an electrolyte solution identical with the brain ash solution, with the exception that the potassium salt was omitted, cell formation was delayed and the cells differed in form from those found in the complete brain ash solution. It should be noted that the lipoids themselves held absorbed potassium ions. Could all the potassium be eliminated, it might be that the power of organization of cells would be entirely lost.

In collaboration with Dr. Otto Glasser of the Cleveland Clinic Radiation Research Laboratory, we subjected the brain lipoid to intense radiation before it was mixed with the brain protein and electrolyte solution, and we found that it had lost the power of organization. No cells were formed. The radiated lipoid material assumed the aspects of a quite different substance. Small globules, apparently resembling neutral fat, appeared, suggesting that radium dislocates the metal elements, viz., the potassium and phosphorus molecules which bind together the delicately poised elements of the cell. Radiation of newly formed cells broke them down. On the other hand, radiating the protein

had no effect. Autosynthetic cells were formed with radiated protein, and non-radiated lipoid as freely as with non-radiated protein. It would seem, therefore, that the lethal effect of radiation must be exerted on the lipoid element of cells including cancer cells, the vulnerable points in the lipoid being probably the phosphorus and potassium atoms.

Cataphoresis measurements have been made from which the electric charge of the protein itself, the lipoid itself, and the organisms, have been calculated. There was a marked potential difference between the lipoid and the protein, and the charge on the cells has been found to vary from 50 to 70 millivolts.

Direct measurements of the electric potential difference of the cells and of the nucleus and cytoplasm were made by introducing electrodes into them. The nucleus was found always to be positive with relation to the cytoplasm, the difference of potential varying between 20 and 30 millivolts.

When "old lipoids," that is, when lipoid material that had been kept over a number of weeks was used, we observed that instead of organized autosynthetic cells, fatty droplets were formed. These fatty droplets, which were similar to those seen after the lipoid had been radiated, were seen also after a cyanide or a toxin was added to the lipoid mixture and after the autosynthetic cells were deprived of oxygen, asphyxiated. This phenomenon apparently corresponds to fatty degeneration and may be produced at will. At Clowes' suggestion, oxygen was bubbled through active lipoid with the expectation that the essential fatty acids would be immediately saturated and rendered inert. This prevented the formation of cells, as anticipated.

The effects of the addition of various agents to the lipoid—protein—electrolyte mixture were as follows:

Both the potential difference and respiration were decreased on the addition of an anesthetic (urethane). (N.B., the effect of ether and chloroform could not be tested as the addition of these substances made the measurement of oxygen consumption impossible.

The addition of salts in various concentrations affected the potential difference of our autosynthetic cells in a manner strikingly similar to the effect of the same concentrations on the potential differences of bacteria (Brown and Broom).

The potential difference of the autosynthetic cells was increased on the addition of thyroxin, of sodium iodide and of glucose.

The potential difference and the respiration were decreased on the addition of morphine.

On the addition of a small amount of strychnine or of alcohol (3 to 5 per cent) the potential difference was increased. On the addition of large amounts of either strychnine or alcohol (50 per cent), the potential difference was decreased. On the addition of a cyanide or of a toxin the potential difference was decreased to zero.

A mixture of the lipoid and protein of a human brain with the electrolyte solution produced a highly organized cell with active division. A mixture of the lipoids extracted from a cancer with proteins and electrolytes produced a bizarre appearance characterized by the presence of many fatty droplets.

Measurements of the iodine number showed that brain lipoid has the highest iodine number and cancer tissue the lowest of any of the tissues measured. On standing or on being oxygenated, as suggested by Clowes, the brain lipoid lowers its iodine number.

Of special significance was the finding that the brain-lipoid-brain-protein-electrolyte mixture produced urea.

From these experiments it is seen that the autosynthetic cells exhibit the three fundamental qualities of living protoplasm: irritability, respiration, and reproduction.

While these results afford no final proof as to the mechanism of the formation of cancer cells by changing the structure of living cells, it offers an analogy and a parallel.

The value of a theory lies in the number of phenomena it interprets and in the number of productive hypotheses it suggests.

What known facts are harmonized by this point of view regarding the formation of cancer cells?

First of all we have shown by our experiments that cells of the highest order with a high degree of differentiation may be reduced to cells of a lower order having only growth and no function. One could suppose that comparable physical changes might be wrought in cells in situ by repeated physical, chemical, or radiation injury, even to the point of a complete breakdown and resynthesis in situ; in other words that any cause which produces a change in the potential of the cells might result in a partial change of the side chains, whose construction and presence depend on an adequate electric potential.

The potential in any given cell may be lowered by any change of the structure of the cell which falls short of a death-producing change with the resynthesis of the cell to a status below that of function and above that of fatty degeneration, namely, at the level of growth only. Again, one may interpret the effect of infection and its toxins on the basis of the behavior of our autosynthetic cells when toxins are added to the brain-lipoid-brain-protein-electrolyte mixture. In our experiments this addition of a toxin interfered with the formation of the autosynthetic cells and induced fatty degeneration. In like manner the local toxins of a chronic infection of a tissue might, by chance, cause just enough impairment of the organizing power of the lipoids in the normal cell to reduce the differentiated cell to a level below that of the normal cell, to that of a cell with growth only, or a cancer cell.

There are, however, other chemical causes of cancer than those produced by bacterial toxins. Cancers are especially prone to form in the presence of acid secretions, as for example, in the acid stomach and the acid large intestine, as contrasted with the almost complete immunity of the alkaline small intestine. Cancer tends to appear on mucous membranes which are chronically infected and show acidity, as on the cervix in chronic cervicitis, associated with, or without lacerations; in the bladder in the presence of acid urine, especially when it is associated with calculus.

Here obviously we have the factor of a change in the hydrogen-ion concentration. In our experiments it was shown that a change of the pH to above or below an optimum level lowered the power of the lipoids to form autosynthetic cells and a like change in the pH of the autosynthetic cells already formed caused a lowering of their form to a lower dynamic level. So we may think of a continued change in the pH as a strong factor in reducing the highly differentiated molecules of the normal cells to a lower level, that of growth only; i.e., to the cancer level.

Then again there is a not inconsiderable group of cancers caused by radiation: solar radiation, *x*-ray and radium radiation, and even possibly by mitogenetic radiation. Our experiments on the effects of radiation on the lipoid fraction of autosynthetic cells showed a progressive lowering of the organizing energy-transforming power, exhibiting every grade of change down to fatty degeneration and total loss of the power of forming cells. This offers one interpretation of the incidence of cancer following radium and thermal burns, and very likely of the effect of excessive solar rays.

It may be argued that radiant energy causes cancer by first producing scars; but a scar is a sequel to the reduction in the level of differentiation of the cells affected by radiation toward malignancy or fatty degeneration or death.

What analogies or parallels do this theory and our researches offer as to the dynamics of the cancer cell? It is generally thought that the cancer cell has abnormally great vigor and high dynamic qualities, for it always kills its host, there-

fore it would appear to be a stronger cell with respect to its dynamic power than any normal cell; and yet the conception here proposed implies that the cancer cell is a cell of lower dynamic order and that its existence is possibly due to a partial lipoid degeneration of normal cells. Cancer in its very origin enjoys an advantage not possessed by bacteria: the cancer cells being derived from the cells of the host set up no antibodies in their host; they are to a great degree in chemical and physical equilibrium with their host. The cells of the host and the cells of the cancer fraternize completely so the cancer unlike bacteria encounters no resistance in the host. That cancer cells are not super-cells as to their dynamics is seen from the fact that, as we have stated, cancer cells cannot compete with the growing power of embryonic tissue, for no cancer exists in embryonic life.

Again, cancer cells are decisively defeated by all the tissues and cells having a higher metabolism, such as muscle cells, heart muscle, voluntary muscle, smooth muscle. Cancer cannot attack the cells of a normal thyroid or those of a hyperplastic gland. Cancer does not attack the active brain cells. Thus cancer is inferior in energy to the vigorous fetal period and to the more active cells throughout life. Cancer cannot arise spontaneously in undamaged tissue, but arises after a certain degree of reduction of vigor by virtue of age; and even then it appears principally in the tissues or organs of a lower dynamic order. But cancer cells arising in early life or in vigorous individuals usually show a higher order of growth-energy. This would be expected on the basis of our experiments. In the aged, cancer grows slowly. It seems as old and as senile as its host.

On the other hand, normal cells have but little growth energy but possess great functional energy, hence a relatively low order of growth-energy in cancer cells is required to compete successfully with the very low growth-energy of differentiated cells. Hence there comes the suggestion that the overwhelming success of cancer cells in destroying the body is due to "unpreparedness" for growth competition on the part of the tissues and organs rather than to a higher order of dynamic attack.

Another pertinent consideration is that in the formation of autosynthetic cells the quality of the lipoid fraction extracted from the various organs and tissues shows in its power to effect the synthesis of cells the dynamic level of the tissue from which it was obtained.

We have seen that the lipoids extracted from the brain have the highest power of forming autosynthetic cells; that the lipoids from other organs have little or no power of organization and especially is it significant that the lipoids extracted from cancer are of the lowest order as compared with those extracted from normal organs or tissues. Cancer lipoid can form no semblance of cells, but is of the order of neutral fat. The significance of the fact that cancer cells are largely anaërobic is not now discussed.

Finally but by no means of least significance is the fact that the iodine number which is an index of the power of a substance to create oxidation, to transform energy, showed the lipoid extracted from cancer to have negligible powers of oxidation. Cancer cells, therefore, seem to be of a low order, just as the autosynthetic cells are of a low order.

Normal cells show respiration, irritability, and reproduction. Autosynthetic cells show respiration, irritability, and reproduction. Autosynthetic cells and cancer cells alike are cells which have been reduced below the level of specialized function but lie above the level of fatty degeneration. That is, the autosynthetic cell and the cancer cell, like the fertilized ovum, lie in the zone of growth alone.

No final conclusions are drawn.

PROPERTIES OF AUTOSYNTHETIC CELLS FORMED IN THESE EXPERIMENTS

Nucleation.
Growth.

Division by (1) fission, (2) budding.
Respiration, respiratory quotient, average 0.8.
Stainability.
Motility.
Production of urea.
Electric charge, average 50 millivolts.
Difference of potential between cytoplasm and nucleus, average 20 millivolts.
Disintegration when potential difference reaches zero.
Decreased potential and respiration on addition of narcotic or anesthetic.
Increased potential on addition of thyroxin, of sodium iodide, of glucose.
Decreased potential and respiration on addition of morphine.
Increased potential on addition of small amounts of strychnine.
Decreased potential and respiration on addition of large amounts of strychnine.
Increased potential on addition of alcohol, 3 to 5 per cent.
Decreased potential on addition of alcohol, 50 per cent.
Decrease of potential to zero and cessation of respiration on addition of cyanides and of toxins.
Decrease of potential to zero and cessation of respiration after radiation.
Tenure of "life" for two and one-half months (to date) by repeated addition of protein to culture.
Radiation of lipoids separately prevented formation of cells on mixture with protein and electrolytes.
Radiation of protein and of electrolytic solution separately had no effect on cell formation.
After exhaustion of rabbits by prolonged insomnia or by certain diseases bizarre forms were produced not at all resembling cells formed from lipoid and protein of normal brains.
After radiation, exhaustion, and asphyxiation, fatty droplets appeared suggesting the occurrence of fatty degeneration.
Lipoid, protein, and ash solution of a cancer did not produce cells but a bizarre structure characterized by the appearance of many fatty droplets.
Lipoids and proteins from a human brain produced highly organized autosynthetic cells showing active division.

SUMMARY OF RESEARCHES TO DATE

Cells were formed in a mixture of brain lipoid, the protein of any organ, and brain ash (electrolyte) solution.

These cells are designated autosynthetic cells.

The lipoid was extracted with ether from dried fresh brain.

The protein was extracted with salt solution from the residue remaining after the lipoid was extracted.

The brain ash (electrolyte) solution consisted of a solution in distilled water of various salts in the proportions in which they are present in the brain.

No cells preëxisted in the sterile solutions used.

THE DIAGNOSIS AND TREATMENT OF ACUTE CRANIOCEREBRAL INJURIES

A COLLECTIVE REVIEW*

(PART I)

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THE number of acute craniocerebral injuries is increasing yearly, the increase being due to the use of high speed vehicles of conveyance, especially the automobile and aeroplane, and the mechanization of industry. That the automobile is becoming relatively a more frequent cause of acute craniocerebral injuries is exemplified by Vulliet's[1] investigations. He found that the percentage of craniocerebral injuries admitted to the hospital in the "pre-automobile era" (in the years 1896 and 1897) was 0.86, whereas the percentage of these cases admitted in recent years (in the years 1927 and 1928) was 2.5, relatively four times as many cases. In a series of 530 cases of craniocerebral injuries reported by Crandon and Wilson,[2] in 1906, a fall was the etiological factor in 80 per cent, whereas in McClure and Crawford's[3] more recent series of cases the automobile was responsible for 54.2 per cent of the injuries, and falls and blows were the cause in 20 and 18.4 per cent, respectively (Chart 1).

CHART 1

RELATIVE CAUSES OF CRANIOCEREBRAL INJURIES

Author	Total No.	Year	Automobile (Per Cent)	Street Car (Per Cent)	Train (Per Cent)	Falls (Per Cent)	Blows (Per Cent)	Gunshot (Per Cent)	Unknown (Per Cent)	Miscellaneous (Per Cent)
Crandon and Wilson	530	1906	....	....	....	80				
Besley	1000	1916	....	....	....	38.4	31.1	3.8	26.7	
Lecount and Apfelbach	504	1920	8.8	11.4	....	23.8	9.4	....	29.6	3.3 Chiropractors
Stewart	6135	1921	23.8 Motorcycle 3.5	9.4	3.2	33.8	21.8	1.6	...	1.3
Connors	336	1927	34.2	6.5	....	30.3	8	....	14.5	3.6
Vance*	512	1927	36.8	3.8	....	29.8	8.9	....	19.5	
McCreery and Berry	520	1928	21.1	2.6	....	34.6	11.9	....	26.9	
McClure and Crawford	441	1928	54.2	2.3	.2	20	18.4	.4	....	3.4

* Autopsy Series.

The present-day conception of craniocerebral injuries differs considerably from that held prior to the last two decades. Prior to this time more attention was paid to the injury of the cranium, which injury was considered more important than the injury to the brain, which is contained

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within the cranium. Even though at the present time the degree of cerebral injury is considered the all important factor in craniocerebral injury by most physicians, there is still the tendency among laymen and insurance companies and unfortunately among certain practitioners to place more stress on injury of the rigid skull than injury of the delicate cranial contents, the brain. Trotter,[4] in discussing the evolution of head injuries, states that our knowledge of head injuries may be divided into three developmental stages. (1) The early period, which lasted up to the last third of the nineteenth century, was characterized by injuries of the skull dominating the subject of head injuries. (2) The middle period, that which extended from the last third of the nineteenth century up until about the beginning of the present century, was characterized by the experimental physiological advances made by the study of intracranial physiology. As the result of the researches of Horsley, Hill, Kocher, and Cushing, the importance of the venous side of the circulation as regards cerebral symptoms was emphasized. (3) The modern period dates from the beginning of the present century and is characterized by the realization that variable degrees of injury of the cerebrum may occur and that the cerebral injury is responsible for the symptoms. The degrees of injury are variations in the degrees of contusion of the brain substance. That lesions of the skull are of relatively little importance in acute craniocerebral injuries has been emphasized by Newell,[5] Trotter,[4] Arnaud and Albert-Crémieux,[6] McClure and Crawford,[3] Vance,[7] Green,[8] Holbrook,[9] and Symonds.[10] Fay[11] states, "Fractures of the skull are rarely, if ever, the cause of death, although it is conceivable that a spicule of bone may be driven into the medulla and thus terminate the patient's life. The vast majority of cases that die from head injuries succumb to intracranial pressure or hemorrhage." This differentiation may appear didactic because as a rule an injury which is severe enough to cause a fracture of the cranium will also produce cerebral damage. The symptoms, however, in such a case are due to the cerebral injury, and it is the injury to the cerebrum and not to the cranium (except in depressed fractures) which requires treatment. On the other hand, simple fractures of the skull do occur in which there is no associated cerebral injury and vice versa, extensive cerebral injuries may be present without any concomitant lesions of the cranium. In a series of autopsies reported by Vance[7] with special reference to fracture of the skull, brain lacerations were found even though a fracture of the skull was not present. In Vance's[7] series of cases these were invariably produced by contrecoup violence, usually resulting from a fall. In a series of 441 cases of craniocerebral injuries reported by McClure and Crawford,[3] 172, or 39 per cent, were unassociated with skull fracture.

In reported series of cases there is considerable variation in the age incidence of craniocerebral injuries. McClure and Crawford[3] found the average age in their series to be thirty years. In Connors'[12] Stewart's,[13] and Vance's[7] series of cranial fracture, the age incidence varied considerably. In Vance's[7] series of 507 cases, the greatest number (22+ per cent) in any one decade was between the ages of forty and fifty years. Stewart[13] in his series of cases found that the average age was thirty-six, whereas Connors[12] found the greatest number (22+ per cent) occurred between one and ten years. There is no apparent reason why such a great discrepancy concerning the age incidence should exist.

CLASSIFICATION OF CRANIOCEREBRAL INJURIES

1. Those with cerebral injury either associated with or without cranial injury.
    1. Concussion
    2. Edema
    3. Contusion
    4. Laceration
    5. Hemorrhage

a. Intradural
b. Extradural

II. Those without brain involvement.
1. Scalp wounds
2. Skull fracture
a. Vault
b. Base
c. Simple
1. Linear
2. Comminuted
d. Depressed
e. Compound

I. CEREBRAL INJURY WITH OR WITHOUT CRANIAL INJURY

1. *Concussion*

There is considerable controversy at the present time among physiologists, clinicians, and pathologists concerning the use of the term concussion. The controversy has arisen largely because of the indefiniteness of the term. If it is kept in mind that concussion is a clinical syndrome which is based upon no pathologic findings, but upon definite clinical symptoms and signs together with a typical clinical course, its use seems justifiable. Concussion is in reality a physiologic and not an anatomic lesion in that no changes can be demonstrated in the cerebrum. Miller[14] defines concussion as a condition which is characterized by "a group of symptoms which are the result of a temporary inhibition of cortical function with or without stimulation or inhibition of one or more of the medullary centers, but which are not accompanied by pathologic lesions." A number of theories have been advanced to explain the condition, concussion. Duret,[15] Heise[16] and Symonds[10] believe that a generalized cerebral anemia is responsible for the clinical symptoms. Tilmann[17] is of the opinion that as a result of the tearing apart of the gray and white matter there occurs a difference in their specific gravities. The fact that a rapid recovery occurs in most cases of concussion, however, does not support this theory. Rahm[11] believes that as a result of the blow there is a new arrangement of the lipoids, protein molecules, and electrolytes in the cerebral cells. Knauer and Enderlen[19] found experimentallythat following a severe blow a rapid acidification of the cerebral cortex occurred. Relatively recently Vara-Lopez[20] demonstrated that in experimentally produced concussion there was a decrease in the hydrogen ion concentration of the spinal fluid, occurring within two minutes after the trauma. In each instance the hydrogen ion concentration had returned to normal after twenty-four hours. Henschen[21] believes that concussion is produced by interference with or interruption at the synaptic junctions of the subcortical centers within the midbrain. These theories are merely speculative and at the present time no proof has been offered concerning the exact cause of the symptoms which are present in concussion. Miller[14] attempted to produce concussion experimentally in animals by single severe or repeated light blows or by the application of an electric current to the medulla. He found that early in the stage of what he considered was concussion in animals there was a stimulation of the medullary centers, especially an increase in respiratory rate and a rise in blood pressure. As the concussion increased, the medullary centers became inhibited and depressed, resulting in an inhibition or paralysis of the respiratory center. Miller[14] was able to demonstrate quite definitely that cerebral anemia was not the cause of concussion. When death did occur, it was due to paralysis of the respiratory center, but as it was temporary, life could be maintained by artificial respiration. He believes that the condition is due to a molecular disturbance of the cell as no gross lesion was demonstrable microscopically. Jackson[22] found experimentally that pressure on the medulla produced the following phenomena: first, an increase in respiration, a slight rise in blood pressure accompanied by a normal pulse rate, and, later, a decrease in respiration, a fall in blood pressure, and a marked slowing of the heart rate.

Concussion is characterized by immedi-

ate and temporary unconsciousness, usually followed by headache, nausea, and occasionally vomiting. Characteristically, there is a rapid recovery from all symptoms. Whereas most patients with concussion recover, it infrequently occurs that patients die without recovering consciousness and in whom at necropsy no gross lesions can be demonstrated. Supposedly these individuals die from concussion. In McClure and Crawford's[3] cases there were 351 cases of concussion, 257 of which were associated with skull fractures and 94 associated with no lesion in the cranium. In a series of 507 autopsies reported by Vance,[7] death from cerebral concussion occurred in 139, or 27.4 per cent; 86 died within a few minutes; 34 in from one to four hours; 11 in from five to ten hours; and in 8 the duration was unknown. Ritter and Strebel[23] are of the opinion that a concussion of the medulla oblongata occurs more frequently and is more important than concussion of the cerebrum. In an analysis of 349 cases admitted to the Zurich Surgical Clinic from 1919 to 1924, 95 cases (27.22 per cent of the entire number of cases, or 83.3 per cent of the true concussions) showed evidence of involvement of the medulla oblongata. Ritter and Strebel[23] believe that concussion of the medulla is evidenced by respiratory and circulatory disturbances, vomiting, blood pressure changes, and unconsciousness. In all cases there was immediate unconsciousness, which in the majority of cases lasted only a few minutes, and never lasted more than five hours. In the majority of cases a retrograde amnesia, present in 63.1 per cent, was associated with unconsciousness. There was an increased pulse rate in 57.9 per cent. Differentiating points between concussion of the medulla oblongata and that of the cerebrum are: in the former the manifestations are more varied, the symptoms appear more slowly, and sequelae occur more frequently. The amount of trauma necessary to produce a concussion of the cerebrum seems to be greater than that which would produce a concussion of the medulla oblongata. Jackson[22] demonstrated experimentally that pressure over the medulla produced definite symptoms (first, stimulation in respiration and rise in blood pressure; later, decrease in respiration, fall in blood pressure and slowing of pulse rate), whereas pressure over the temporal and parietal regions of the brain produced no change in respiration, blood pressure, or pulse rate.

Concussion of the cerebrum occurred in only 4.29 per cent of the entire number of Ritter and Strebel's[23] cases (13.19 per cent of the cases of concussion). Unconsciousness did not develop as frequently as in concussion of the medulla. It was absent in 20 per cent of the cases. In 80 per cent of the cases in which it was present it occurred immediately, was deeper, and lasted definitely longer than in concussion of the medulla. It lasted more than five hours in 60 per cent of the cases. In only 20 per cent of the cases had unconsciousness disappeared within three hours. Retrograde amnesia was present in 66 per cent of the cases. Vomiting occurred in 26 per cent of the cases and the temperature was always increased. Clinically, it is particularly important to recognize a cerebral concussion in order that proper therapy may be instituted. In all individuals in whom unconsciousness has occurred irrespective of the length of time which it has persisted, a period of rest is imperative in order to prevent the development of sequelae.

2. *Edema*

Edema of the brain has been recognized by pathologists for a long period of time. Its significance has not been appreciated by clinicians until relatively recently; in fact, not until the introduction of the dehydration therapy, which is directed entirely against "wet brain." Le Count and Apfelbach[24] in a study of 504 postmortem examinations of patients with craniocerebral injuries state that the most frequent change in the brains which they

studied of patients dying with fracture of the skull was traumatic edema. They describe the convolutions as being flat and the cerebral veins relatively empty and flat and state that the fluid in the leptomeninges is greatly diminished. Apfelbach[25] two years later in describing the edema of the cerebrum associated with craniocerebral injuries states that it characteristically is a generalized edema and not a localized one about contusions. He found that at autopsy the dura was of drum-like tenseness due to the edema, the tenseness varying with the amount of intracranial tension. The brain when removed from the cranial cavity was found to be soft and easily lost its form when laid on a flat surface. After it had been hardened for several days there was increased difficulty in cutting it, the lateral ventricles were closed, and a stippling of the brain substance by small intracerebral blood vessels was demonstrable. Microscopically, the perivascular lymph sheaths were distended and there were empty spaces between the fibers and cells, the latter being further apart than normal. Determination of the water content was made from the brains of 26 patients who died from craniocerebral injuries (Apfelbach'[25]). It was found that there was an increase in the amount of water above the normal content of from 3 to 45 gm. or as high as 3.7 per cent. Edema in Apfelbach's[25] series of cases was found most frequently in the brains of persons who died from within several hours after the accident up to the second or third day. Green[8] emphasizes the importance of cerebral edema and the necessity of its prompt treatment. He states that relatively slight injury to the cranium of individuals suffering from cardiorenal disease is sufficient to produce cerebral edema. The work of Fischer[26] is interesting in connection with cerebral edema. Fischer[26] states that edema occurs whenever in the presence of water the tissue colloids are increased and that an increase in acidity causes an increase in the accumulation of colloids. The increased acidity may be due either to increased production or insufficient elimination of acids. Henschen[21] has found that in patients recovering from concussion and contusion of the brain there is an increased secretion of lactic acid, acetic acid, and phosphoric acid in the urine. Vara-Lopez[20] has found a decrease in hydrogen ion concentration of the cerebrospinal fluid in concussion. Knauer and Enderlen[19] state that an acidification of the cerebral cortex occurs in cerebral concussion. It is possible that the decrease in the hydrogen ion content of the cerebrum may be responsible for the cerebral edema. That the majority of symptoms in craniocerebral injury are the result of increased intracranial pressure is accepted by most authorities today. This increase in intracranial pressure is in by far the majority of cases the result of cerebral edema, which in a relatively short time produces a vicious circle; i.e., as the result of the increased intracranial pressure there is interference with the venous return which hinders absorption of the cerebrospinal fluid. This results in actual increase in the amount of cerebrospinal fluid. As the condition progresses, the arterioles become compressed, producing a cerebral anemia.

3. *Contusion of the Brain*

Contusion of the brain frequently follows trauma to the head. Le Count and Apfelbach[24] in their study of 564 brains of patients dying with skull fractures found that contusion of the cerebrum, when present, was usually wedge-shaped and that the brain was infiltrated with blood for a depth of from 2 to 4 cm. over an area with an outside diameter of from 4 to 5 cm. This type of contusion was found in 49.2 per cent of their series, in 73.3 per cent of which it was due to a contrecoup injury. Similar areas of localized contusions are reported by Arnaud and Albert-Crémieux.[6] Cerebral contusions occurred in only 7.03 per cent of McClure and Crawford's[3] cases, which, however, were observed clinically and not at necropsy. Contusion

is of importance, because it is frequently the cause of death. According to Vulliet,[1] massive cerebral contusion was the cause of death in 18.7 per cent of 96 cases observed by him, whereas Trotter[4] is of the opinion that contusion of the brain is probably the most common cause of death and that most of the symptoms produced by cerebral injury are the result of contusion. Symonds[27] differentiates between a major and a minor type of contusion, the difference being one of degree. He considers clouding of the consciousness or stupor as a distinguishing feature of major contusions. The patient does not recover, but remains stuporous, restless, and irritable. Patients with minor contusion complain, however, of headaches, giddiness, and mental disability. In contrast to concussion the symptoms of contusion usually develop after a latent period of hours or days. The headache is dependent upon changes in posture. Stupor, according to Symonds, is not a prominent part of minor contusion. Contusion is associated pathologically with varying degrees of hemorrhage, varying from small petechiae to rather extensive effusion. Apfelbach[25] has shown that characteristically the hemorrhage associated with contusion is greater, within certain limits, the longer the patient lives after the injury. The brain of an individual who died shortly after the injury shows evidence of contusion which is superficial, whereas if life is continued for from one to two days, larger contusions are found. This Apfelbach[25] believes might be due to the persistence of the bleeding after the injury has ceased.

4. *Lacerations*

Laceration of the cerebrum represents a more extensive injury than contusion. Even though its differentiation from contusion may be an artificial one, the difference being largely of degree, it is, however, deemed advisable to consider lacerations separately, especially in those cases in which there is definite tearing of the cerebral substance as contrasted with the bruising which occurs in contusion. According to Blahd[28] laceration is usually associated with or dependent upon fracture of the skull. In McClure and Crawford's[3] series of 441 cases of craniocerebral injuries treated at the Henry Ford Hospital there were 54 with laceration of the cerebrum, 5 without skull fracture, and 49 associated with fracture. In addition, there were 5 cases of laceration and hemorrhage, all associated with skull fracture. In 504 necropsy examinations of patients with skull fracture reported by Le Count and Apfelbach,[24] severe laceration of the brain measuring 40 cm. in diameter and extending into the brain substance for from 4 to 5 cm. was found in 64 instances (slightly over 10 per cent). In 15 of these the lacerations extended into one of the lateral ventricles. In 39 bleeding continued intracerebrally for several centimeters beyond the laceration. Thirty-six of the lacerations occurred in the frontal lobe, 3 in the occipital lobe, and all except 8 were contrecoup injuries. Bagley,[29] on the other hand, believes that lacerations of the cortex are the result of direct force of the blow and may be associated with simple or compound fractures of the skull, but frequently occur without fracture of the skull. The tips of the temporal and bases of the frontal lobes were most often the seats of laceration in Bagley's[29] experience. Vance[7] classifies cerebral lacerations associated with skull fractures into direct lacerations and contrecoup lacerations, of which the contrecoup variety occurs more frequently than the direct. In his series of 512 necropsies of individuals with fracture of the skull, 24 died of cerebral lacerations. Of this number 6 had unilateral, whereas 11 had bilateral contrecoup lacerations; 4 had direct lacerations and 3 direct and contrecoup lacerations. In Le Count and Apfelbach's[24] and Vance's[7] series contrecoup laceration occurred as a rule when the skull as a moving object struck against a fixed object. This is explained by Le Count and Apfelbach[24] by the fact that during the movement of the head the brain lags

behind the more rapidly moving cranium and at the moment of the impact the brain is closer to the cranium opposite to the point where the violence is applied.

5. *Hemorrhage*

Hemorrhage associated with craniocerebral injuries is of two types, intradural and extradural. Associated with every cerebral injury from the slightest contusion to the more extensive laceration, there are varying degrees of hemorrhage. (a) *Intradural* hemorrhage occurs as a result of cerebral contusion or laceration, whereas extradural hemorrhage occurs as a result of injury to the middle meningeal artery, one of its branches, or rarely the lateral venous sinus. Due to the work of Kocher,[30] the clinical significance of extradural hemorrhage has probably been overemphasized. By this I do not mean that the presence of an extradural hemorrhage is not important, but because localized hemorrhage is so amenable to surgical therapy the relative importance of this type of intracranial lesion probably has been overemphasized by surgeons. Localized hemorrhages occur much less frequently than do the other types of lesions previously discussed. In 96 cases of craniocerebral injury reported by Vulliet[1] a localized hematoma occurred in only 2 instances. Massive hemorrhage associated with cerebral lacerations occurred in only 5 of McClure and Crawford's[3] 441 cases of craniocerebral injuries. Apfelbach[25] states that hemorrhage may occur at the junction of the gray and white matter of the cerebral substance without any gross evidence on the surface of the brain opposite the point of hemorrhage. The hemorrhage may extend from here out toward the periphery. In Vance's[7] 512 necropsies, 312 deaths were caused by subdural hemorrhage, the majority of the patients dying within twenty-four hours. Fractures associated with the subdural hemorrhage occurred most often in the posterior and lateral portions of the skull. In the 132 cases hemorrhage was produced by contrecoup lacerations in 85, by direct laceration in 21, and by contrecoup and direct laceration combined in 21 cases. Vance[7] considered a case of having subdural hemorrhage whenever there was enough hemorrhage to produce compression of the brain. The average weight of the subdural coagulum was 6.1 gm. In 100 per cent, 73.8 per cent, and 84 per cent of fractures of the anterior, middle, and posterior fossas, respectively, in Le Count and Apfelbach's[24] series of cases a subdural hemorrhage was found. According to Jackson[22] 20 per cent of the cases of craniocerebral injury which come to autopsy have a middle meningeal hemorrhage with increased cerebrospinal pressure. One hundred and fifteen instances of subdural hemorrhage occurred in fracture of the posterior fossa examined by Vance, or 84.5 per cent. In 98 cases there was an associated subdural hemorrhage in fractures of the middle fossa, or 73.8 per cent, whereas subdural hemorrhage occurred in 100 per cent of the cases of frontal fossa fractures. The importance of subdural hemorrhage and the presence of blood in the spinal fluid has been emphasized by Essick[31] and Bagley,[32] both from a clinical and experimental viewpoint. Essick[31] found experimentally that the injection of laked blood into the subarachnoid space produced a sterile meningitis. Experimentally, Bagley[32] injected blood into the subarachnoid space of 18 adult dogs and 26 puppies. Spasticity occurred immediately after the injection. Many of the dogs died within the first few days. The diminished activity and the poor development of the younger dogs were characteristic. Microscopically, following the introduction of blood into the cerebrospinal fluid there was definite evidence of reaction of the meninges coming in contact with the blood. Subsequently changes in the cortex occurred, and in young puppies moderate dilatation of the ventricle followed. In 6 of the 19 puppies which received injections and in which autopsies were performed, a definite dilatation of the ventricles was found. Subdural hemorrhages are of importance not only

because of the immediate symptoms which may be produced, but because of subsequent lesions. Fay and Winkelman[33,34] have emphasized the importance of diffuse collections of cerebrospinal fluid over the cerebral cortex following subdural hemorrhage with resulting cerebral atrophy as the result of pressure. In addition to the diffuse types of subdural fluid collections following subdural hemorrhage, there are localized lesions first described by Virchow,[35] but not appreciated clinically until recently. These consist of cystic changes in localized hematomas. Valuable contributions to the question of subdural hematoma or chronic hemorrhagic pachymeningitis have been made by Naffziger,[36] Grant,[37] Rand,[38] and Cohen and Elsberg.[39]

(b) *Extradural Hemorrhage:* Extradural hemorrhage is of less importance than subdural hemorrhage in so far as it occurs much less frequently. However, because of the marked increase in intracranial pressure which is produced by an extradural hemorrhage and because of the fact that it is especially amenable to surgical treatment, it is important, from the standpoint of treatment that the possibility of an extradural hematoma should always be considered. The hemorrhage usually occurs from the middle meningeal artery or one of its branches. In most cases the anterior branch of the vessel is the portion most frequently injured, either because of tearing of the vessel by fracture or tearing of the vessel by detachment of the dura from the inside of the cranium. Extradural hemorrhage occurred in 39.4 per cent of the necropsy series reported by Le Count and Apfelbach.[24] In only 52.2 per cent of this group, however, was the hemorrhage large enough to produce an appreciable compression of the brain. Of the large extradural hemorrhages 70.1 per cent were associated with fracture of the middle fossa, 14.4 per cent were associated with those of the posterior fossa, and 9.6 per cent were associated with fractures of the vault, 2.8 per cent with fracture of the anterior fossa. In a series of 507 cases observed at necropsy and reported by Vance,[7] extradural hemorrhage was described in 106. Only 61 (12 per cent of the latter) of these, however, were large enough to prove fatal by cerebral compression. In a series of 233 cases in which a fracture was present in the lateral part of the skull in only 56 (24 per cent) was the middle meningeal hemorrhage sufficient to produce cerebral compression. The greatest number of extradural hemorrhages occurred in Vance's[7] series between thirty and forty years of age, which he believes is due to the fact that the dura is adherent just enough to the skull to allow laceration of the artery, but not adherent enough to prevent its separation from the bone. The extradural hemorrhage in Vance's[7] series of 61 cases originated in the posterior branch of the middle meningeal artery in 25, in the anterior branch in 12, in the main stem in 4, in a branch of the middle meningeal which was not determined in 15, in the anterior meningeal artery in 1, and in the lateral venous sinus in 4.

II. INJURIES NOT INVOLVING THE BRAIN

1. *Scalp Wounds*

The importance of scalp wounds in acute craniocerebral injuries has not been sufficiently appreciated by the medical profession. Weaver[40] emphasizes the proper care of scalp wounds and considers them as potential brain abscesses, as they are frequently the sites through which organisms can gain entrance to the cerebrum. Of 520 cases of cranial fracture reported by McCreery and Berry,[41] in 216 there was an associated scalp wound, 37 of which communicated with the fracture. Sixty per cent of 6117 cases of skull fracture reported by Stewart[13] were associated with lacerations of the scalp, 98 of which occurred in the frontal region, 130 in the parietal, 88 in the occipital, and 55 per cent in the temporal area.

2. *Fractures of the Skull*

There is considerable variance among authors concerning the relative frequency

of fractures of the vault. In general, however, it might be said that statistics based upon necropsy investigations show a relatively low percentage of skull fractures involving the vault. In Vance's[7] series of 512 cases, the vault alone was involved in only 6.7 per cent, whereas the vault and base were involved in 91.9 per cent. In Le Count and Apfelbach's[24] series the vault was involved in 9.9 per cent and the base in 89.8 per cent. In clinical series, however, vault fractures occur more frequently than basal fractures, probably because basal fractures are not diagnosed because of the difficulty in demonstrating them roentgenologically. In McClure and Crawford's[3] clinical series of 441 cases, 85.7 per cent of the cases of fracture were fractures of the vault and only 5.7 per cent were fractures of the base alone. Stewart[13] states that 70 per cent of the linear fractures of the vault extend to the base by the shortest route. Vance[7] explains the higher percentage of basal fractures as compared with those of the vault on anatomical grounds. The vault is stronger and with the exception of the temporal region is of even thickness. The base, however, is of irregular, flat construction, composed of heavy masses of bone weakened by thin plates. He[7] believes, as does Stewart,[13] that in most instances fractures begin in the vault and extend down to the base. The fissures course along between the strong masses of bone and are directed toward the central part of the skull. According to Peet[42] fractures of the vault are the result of localized trauma.

Basal fractures are frequently overlooked, because of the difficulty in diagnosing the condition, largely because of inconstant and indefinite radiographic signs. As evidenced by necropsy examinations of Vance,[7] Le Count and Apfelbach,[24] basal fractures either alone or associated with fractures of the vault are the most frequent type of fracture of the skull. In Vance's[7] series of cases the posterior fossa was involved in 34.8 per cent, the middle fossa in 45.2 per cent, and the anterior fossa in 11.9 per cent of the cases. In Le Count and Apfelbach's[24] series the anterior, middle, and posterior fossae were involved in 12.1 per cent, 32.9 per cent, and 35.3 per cent of the cases, respectively. Because basal fractures are apt to extend either into the nose, nasal accessory sinuses, or the middle ear, the danger of the occurrence of secondary infection of the meninges is especially great. Prognosis should be more guarded in basal fractures not only because of the danger of infection, but also because of associated injury to the cortical centers. Peet[42] believes that fractures of the base are the result of a massive blow, usually much more severe than that responsible for fractures of the vault and are associated with more extensive cerebral injury. Of 39 fractures of the vault reported by Blahd[28] there was a mortality of 13 per cent, whereas in 20 cases of fracture of the base there was a mortality of 65 per cent.

Of the various types of fractures, simple fractures occur most frequently. A simple fracture may produce no symptoms and be of no clinical significance; in fact, the only significant feature about a simple fracture of the skull is an associated cerebral injury. Compound fractures, however, are of definite significance because of the danger of the introduction of microorganisms into the wound and the subsequent infection. The proper care of compound fractures has been stressed by Cushing[43] and others.[44,12] Of 37 operations performed by Thorning[45] in a series of 100 cases of acute craniocerebral injury, 51 per cent were performed for compound fractures. Compound fractures are, therefore, of surgical interest. Depressed fractures are also distinctly surgical and require operative intervention. The fragment because of its direct pressure on the cerebral cortex may give rise to very definite symptoms. Bagley[29] is of the opinion, however, that if the dura remains intact that the depression may be of little significance. Depression occurred in 198 of the 408 fractures of the vault reported by Stewart[13] and

in only 5.1 per cent of 520 cases reported by McCreery and Berry.[41]

DIAGNOSIS

The diagnosis of acute craniocerebral injuries is extremely important. A great deal can be learned from the history. Of paramount importance is the presence or absence of consciousness, as extensive cerebral injury is always associated with unconsciousness. McClure and Crawford[3] believe that the degree and the duration of the primary unconsciousness serve as a fair index to the severity of the injury and probable subsequent course, except in hemorrhage and infection. One of the diagnostic features of concussion is immediate unconsciousness which is invariably present. In McCreery and Berry's[41] 520 cases of skull fracture, 178 were conscious and rational, 23 were stuporous, and 218 were in coma on admission to the hospital. The clinical syndrome, as described by Kocher,[30] of temporary primary unconsciousness followed by a lucid interval later followed by unconsciousness, is characteristic of a rapidly increasing intracranial pressure of a severe degree which is almost invariably associated with intracranial hemorrhage, usually from the middle meningeal artery. These cases, however, are relatively rare as compared with the large number of acute craniocerebral injuries.

The pulse rate has been considered of diagnostic value in acute craniocerebral injuries. Newell places it second to the history. It is now known that too much dependence should not be placed on the pulse rate as there may be little alteration in the pulse early in the condition, changes in pulse rate being the result of considerable cerebral damage and indicating an advanced lesion. It is probably of more value as a prognostic agent than as a diagnostic agent. Fay[11] attached considerable significance to the pulse rate and also the character of the pulse. He believes that a pulse rate of 70 or below is the result of a vagus irritation and the cause should be ascertained. As possible causes one must consider bloody spinal fluid, increased intracranial pressure, edema of the cardiac center, or middle meningeal hemorrhage. In Ritter and Strebel's[23] series of 349 cases of concussion of the medulla oblongata, the pulse rate was slightly increased in 57.9 per cent and normal in 40 per cent. Jackson[22] found experimentally that pressure over the medulla produced at first little change in the pulse rate; later, however, the heart rate became slowed. The pulse rates of patients with acute craniocerebral injuries, when admitted to the hospital, may vary considerably. This becomes self-evident when it is kept in mind that many patients with acute craniocerebral injuries are in shock when admitted. Characteristically the pulse in shock is of a small volume, and the rate is usually increased which is dependent upon the condition of shock and not dependent upon the cerebral injury. The thready pulse which these patients have is the result of lack of resistance in the capillary bed. According to Fay[11] this phenomenon is of extreme importance in that the anoxemia associated with lowered vascular tension predisposes to further edema, because of the increased permeability of the capillaries as shown by Landis.[46] In cases with marked increase in intracranial pressure as seen in hemorrhage from the middle meningeal artery, the pulse becomes definitely slowed due to edema of the medullary centers. This, however, represents an advanced lesion and is always associated with a marked increase in intracranial pressure. Associated with the bradycardia is a definite rise in the blood pressure and unconsciousness. This symptom complex should never be waited for, but the diagnosis of increased intracranial pressure should be made before these symptoms present themselves. In 39 of McCreery and Berry's[41] 520 cases the pulse on admission was less than 60. Twenty-nine of these patients died.

Miller[14] believes from his experimental work that the determination of respiratory rate is of great deal of significance in

cerebral concussion. He was able to demonstrate experimentally that of all the medullary centers the respiratory center was affected earliest by cerebral injury. In less extensive injuries there resulted a stimulation of the respiratory center with an increase in respiratory rate as well as an increase in amplitude. As the injury became more severe, there resulted a paralysis of the respiratory center with cessation of respiration. Jackson[22] found experimentally that pressure over the medulla produced increase in respiration, which was later followed by a decrease. Miller[14] believes that this respiratory paralysis is responsible for the sudden death in concussion. Newell[5] states that as the intracranial pressure becomes increased, respirations become labored and slowed. Fay[11] considers the respiratory rate of extreme importance, especially as regards prognosis. If it is above 26, it frequently indicates cerebral irritation and blood is usually found in the spinal fluid. If the respiratory rates reach 40 per minute, there is indication of severe cerebral damage. The hyperpnea is of importance because of the hyperventilation with the subsequent washing out of the carbon dioxide and the development of alkalosis and edema. Decreasing respiratory rates, according to Fay,[11] are usually the result of increased intracranial tension. In contrast to the experimental results of Miller[14] and Jackson[22] are the clinical findings of Besley,[47] who in an analysis of 1000 cases of skull fracture admitted to the Cook County Hospital in Chicago, found the following: Patients who recovered with fractures of the vault had an average respiratory rate of 24 and those who died had an average rate of 32. Patients who recovered with basal fractures had an average respiratory rate of 24, whereas those who died had an average rate of 40.

Of primary importance as far as diagnosis is concerned Newell[5] believes is the temperature. He states that it is usually subnormal immediately after brain injury, but in mild cases after twenty-four hours it rises to from 99.4 to 100.4°F. It is not clear from his publication whether those cases with decreased temperature were associated with shock or not. Undoubtedly many cases were associated with shock and in all probability the shock was the cause of the decreased temperature rather than the cerebral injury. Symonds[27] is of the opinion also that early in cerebral injuries the temperature is decreased. In Besley's[47] series of 1000 cases of skull fracture the average temperature of those patients who recovered was 100°F., whereas that of those who died was 102°F. In the series with concussion of the medulla oblongata reported by Ritter and Strebel,[23] the temperature on the first day was below 37°C. in 49.4 per cent, from 37 to 38°C. in 21.05 per cent, from 38 to 39°C. in 3 per cent of the cases.

Careful physical examination of the entire body, provided that the patient is not in extreme shock, will yield considerable information concerning the nature and extent of the cerebral injury. In such examination special care should be paid to the ears, nose, and mouth in order to determine whether there is evidence of escaping blood or spinal fluid. Hemorrhage from these natural orifices, unless there is an obvious wound from which bleeding may occur, is indicative of basal skull fracture. Ecchymosis may occur around the eyes or behind the ear, or over the mastoid process (Battle's sign). The prognosis is much worse in those cases in which there is hemorrhage from the ears, nose, or mouth, because of the possibility of organisms gaining entrance to the meninges as a result of the compound fracture. Schuster[48] states that middle ear fractures have a poor prognosis, because this portion of the temporal bone does not heal well, which may result in a permanent communication between the middle ear and the meninges. According to Davis,[49] hemorrhage from both ears is an especially unfavorable sign, the mortality rate in his series being 66 per cent and 39 per cent in cases with bilateral and unilateral hemorrhage, respec-

tively. The danger of meningitis is especially great in cases in which there existed previously an infection of the middle ear, mastoid process, or nasal accessory sinuses. In addition to hemorrhage and discharge of cerebrospinal fluid from the ear, Schuster[48] states that in about 40 per cent of all head injuries there are other symptoms referable to the ear; i.e., impaired hearing, dizziness, and tinnitus. These were the most frequent sequelae in McCreery and Berry's[41] cases, but there was a definite tendency for improvement to take place within eighteen months to two years. The symptoms which persisted after that period of time appeared to be permanent. In Davis's[49] cases of head injury in which there was an associated eighth nerve paralysis, the paralysis was immediate in all cases, and all patients recovered even after long intervals.

A careful neurological physical examination is extremely important and should be repeated frequently in order to detect any progression of the various lesions. In McClure and Crawford's[3] and McCreery and Berry's[41] series of cases the seventh and eighth nerves were more frequently involved than any of the other cranial nerves. Fay[11] considers aphasia as an important localizing sign. Care must be taken not to confuse it with stupor. They can be differentiated by reaction of the patient to an extremely painful stimulus. If the patient is aphasic, he will attempt in the normal manner to remove the stimulus, whereas if he is stuporous, his movements will be purposeless. Examinations of the reflexes, especially the Hoffman and the Babinski reflexes, are particularly valuable according to Fay.[11] In McCreery and Berry's[41] series of 520 cases of skull fracture a negative neurological examination was found in 127. Cranial nerve paralysis occurred in 58 patients, of whom 44 recovered; spinal nerve paralysis in 88 cases, of which 51 were of the flaccid type and 37 merely a weakness. Of the 51 patients with flaccid paralysis, only 3 recovered and 48 died. Of the 37 in whom muscular weakness was demonstrated, 14 recovered and 23 died. The superficial reflexes were decreased in 58; the deep reflexes were decreased in 63 and increased in 79. Abnormal reflexes were present in 62.

Of extreme importance as regards the extent of injury, the progress and prognosis of the case, are the eye manifestations. Changes in the pupils are of great diagnostic and prognostic significance. According to Lyerly[50] the size of the pupil normally seldom varies in the two eyes. Barrie[51] found on examination of 326 recruits with apparently normal eyes an inequality of the pupils in about 10 per cent. Characteristic of pupillary changes in acute cerebral injury are the inconstant findings on repeated and frequent examinations. According to Blakeslee[52] the pupillary changes, which are the most frequent of all eye manifestations, may change in such a way that one or both pupils might assume a different size or shape or become eccentric within a period of a few hours. McClure and Crawford[3] recommend repeated eye examinations, because of the frequent changes which are apt to and do occur in severe acute craniocerebral injuries. The importance of careful examination of the eyes in head injuries is exemplified by Blakeslee's[52] study. In a series of 610 cases of cranial fracture, 475 (78 per cent) manifested eye signs, whereas only 133 (22 per cent) had normal eye findings. Pupillary changes were observed in 378 patients and of this number 179 (47.5 per cent) died. In his series of cases he was able to divide the pupillary phenomena into eight groups: (1) widely dilated pupils with fixation; (2) widely dilated pupils with preserved reaction to light, (3) unilateral and fixed pupils; (4) pupils equal in size and not markedly dilated or contracted; (5) pupils unequal in size and not markedly dilated or contracted; (6) pupils contracted and fixed; (7) pupils contracted with preserved reaction to light; (8) pupils usually dilated with or without light reflex or a dilated pupil with partial ptosis or slight divergent strabismus, associated

with a contralateral upper motor neuron paralysis (partial Weber's syndrome). Macewen,[53] in 1887, stated that unilateral dilatation and fixation of the pupil were associated with fracture of the middle fossa of the skull, and in those cases in which necropsies were obtained, the basal fracture continued into or toward the vertex, and a massive clot in most instances occupied the whole of the middle fossa extending from the petrous portion of the temporal bone to the vertex. In McClure and Crawford's[3] series of cases the pupil was usually dilated on the side of the lesion, and in all patients with dilated and fixed pupils a fatality resulted. Blakeslee[52] states that even though it is generally agreed that a unilaterally dilated and fixed pupil is a localizing sign of epidural hemorrhage, appearing on the side of the hemorrhage and fracture, it may occur in cases with epidural and subdural hemorrhage on the homolateral side, and not infrequently is seen in contrecoup laceration and hemorrhage. Holman and Scott[54] state that a unilateral dilatation and fixation of the pupils almost invariably occur on the side of the lesion and are usually the result of progressively increasing cerebral compression from hemorrhage. McCreery and Berry[41] found in their series that a unilateral enlargement and fixation of the pupil were indicative of a lesion on the homolateral side.

Eye manifestations in cerebral injuries are extremely important as regards prognosis. Of 610 cases of fracture of the skull observed by Blakeslee,[52] 78 per cent showed eye signs, of which number 79.5 per cent consisted of pupillary changes. Forty-seven and five-tenths per cent of the patients with pupillary changes died. In a series of 75 cases of skull fracture in which death occurred in 24, Cohen[55] found the following pupillary changes: in the 24 fatal cases the pupillary findings were normal in 6 and abnormal in 18, whereas in the 51 non-fatal cases the pupillary findings were normal in 44, abnormal in 4, and in 3 the findings were not stated. In McCreery and Berry's[41] series of 520 cases of cranial fracture the pupils were normal in 284 of which number 231 recovered and 53 died. There were pupillary changes in 231 patients of whom 151 recovered and 80 died. Of Stewart's[13] 617 cases of skull fracture, the pupils were normal in 396 and the pupillary findings were abnormal in 221. Of the patients in Blakeslee's[52] series with widely dilated and fixed pupils 94.5 per cent died. All the patients in Stewart's[13] and McClure and Crawford's[3] series who had widely dilated and fixed pupils died. All those in Stewart's[13] series presenting these phenomena died within five minutes to two hours after admission to the hospital. Walton[56] found a fixation of the pupil in 39 of his 53 fatal cases. Nicols[57] states that fixation of the pupils is a much more serious omen than is inequality of the pupils. Of 54 patients having skull fracture in whom there was a fixation of the pupils, 47 died. Cohen[55] and Gunn[58] state that inequality combined with fixation of the pupils is common in fatal cases of head injury, whereas these signs are found infrequently in those patients who recover. Unilateral dilatation with fixation of the pupil is a less serious sign than is bilateral fixation and dilatation. In Blakeslee's[52] series, the mortality was 50 per cent. These findings are not only of prognostic, but also of diagnostic value in that the dilatation and fixation almost invariably occur on the side of the injury and are usually the result of hemorrhage. In Macewen's[53] series in which these ocular phenomena were present, there was invariably a fracture of the middle cerebral fossa and in those cases in which a necropsy was performed, a large hematoma was found. McClure and Crawford[3] and McCreery and Berry[41] found that unilateral fixation and dilatation of the pupil occurred on the side of the cranial cerebral lesion. Similar observations have been made by Holman and Scott,[54] Blakeslee,[52] Lyerly,[50] and Gunn,[58] who also state that the phenomenon is usually caused by intracranial hemorrhage.

Less ominous is bilateral dilatation of the pupils without fixation. In Blakeslee's[52] series there was a 30 per cent mortality in those patients presenting these ocular signs. In Stewart's[13] series, 63 patients showed no abnormal findings except inequality of the pupils, 46 of whom recovered and 17 died, whereas in McCreery and Berry's[41] 41 patients in whom an inequality of the pupils was present, only 5 recovered and 36 died. Of the patients in Blakeslee's[52] series presenting inequality with neither dilatation nor contraction of the pupils, 44 per cent died, whereas of those in whom the pupils were equal and neither dilated nor contracted, 32 per cent died.

Contraction of the pupils is found less frequently than dilatation in cases of cerebral injury. In Blakeslee's[52] series of 378 patients exhibiting pupillary changes, myosis was present in only 62 (16.7 per cent). Stewart[13] is of the opinion that the pupil is first contracted and later becomes dilated. Of Blakeslee's[52] 62 patients with myosis, in 20 the pupils were fixed (mortality rate 76 per cent), and in 42 the pupils reacted to light (mortality rate 40 per cent). According to French[59] bilateral pinpoint pupils are suggestive of pontine hemorrhage, whereas Sharp[60] believes that a pinpoint pupil is due to cortical irritation by a supracortical hemorrhage.

The exact mechanism of the pupillary changes is not entirely understood. One recalls that dilatation and contraction of the pupils are produced by the muscles of the iris, which has a dual nerve supply. The oculomotor nerve supplies the circular muscle, and stimulation of it produces contraction, whereas paralysis causes dilatation of the pupil. The dilator papillae muscle is supplied by sympathetic fibers which arise in the ciliospinal tract of the cervicothroacic cord. Stimulation of these fibers produces dilatation and paralysis causes contraction of the pupil. Walton[56] believes that processes, either irritative or paralytic, in the ciliospinal tract and not lesions of the third cranial nerve are responsible for pupillary changes. Holman and Scott,[54] on the other hand, believe that mydriasis associated with cerebral injury is usually the result of injury or compression of the third cranial nerve. In addition to lesions in the efferent nerve, it must be kept in mind that injury to the afferent fibers within the optic nerve may produce pupillary changes by breaking the reflex arc.

Nystagmus is of less significance in cerebral inury than are pupillary changes. It was observed in only 53 patients in Stewart's[13] series of 6135 cases of head injuries. Of these 53 patients, 30 died and 23 recovered. The nystagmus was toward the injured side in 23 cases and toward the uninjured side in 11 cases. McClure and Crawford[3] state that nystagmus is an unfavorable sign. Of Blakeslee's[52] 475 patients of skull fracture in whom there were positive eye findings, nystagmus was found in only 13. Four (30 per cent) of these 13 died.

There is some controversy concerning the value of eye ground examination in craniocerebral injury. In Blakeslee's[52] series of cases, papillitis with slight swelling of the vessel together with slight edema and obliteration of the disc margin was recorded in only 18 of the 610 cases of fracture of the skull. Thirty-nine per cent of these patients, however, died. Thorning[45] is convinced that eyeground examinations are of relatively little value. In 4 of the 12 cases examined by him, the fundic changes were definite, but in these cases the clinical signs were so pronounced that the condition of the optic disc did not influence the treatment. There were other cases in which the signs were indefinite from the standpoint of the eyegrounds, but in which there were additional diagnostic signs and in which at operation lesions producing increased intracranial pressure were found. Gunn,[58] on the other hand, believes that early changes in the optic disc are of value. He states that there is no noticeable change within six hours following injury. The first change is an increase of the size of the retinal vein, which is accompanied by a hyperemia of

the disc and followed shortly by an edema of the nasal half of the disc. According to Gunn[58] and Cohen,[55] choked disc is never seen in cases of acute craniocerebral injury. In McClure and Crawford's[3] series a choked disc was a late phenomenon, but engorgement of the veins and a haziness of the disc margin occurred relatively early. According to McCreery and Berry[41] a fundic examination is, with the exception of spinal tap, the simplest and most direct way of determining increased intracranial pressure. In Cohen's[55] series of 24 fatal cases of skull fracture, the fundus was normal in 8; there was neuroretinitis in 3; mild bilateral papillitis in 3; mild unilateral papillitis in 1; moderate papillitis in 1; retinal hemorrhage in 2, and no examination in 5. The fundic changes in the non-fatal cases were normal in 35; there was unilateral primary atrophy in 3, and mild papillitis in 3. Green[8] states that the retinal changes which occur as the result of progressive increases in intracranial pressure are: (1) engorgement of the retinal veins and increase in size of the retinal artery; (2) obliteration of the outline in first the nasal and later in the temporal sides of the disc; (3) complete obliteration of the disc. If the edema is over two diameters, a choked disc may be said to be present.

BLOOD PRESSURE

To Kocher[30] belongs credit for calling attention to the rise in blood pressure which accompanies rapidly increasing intracranial pressure and which is dependent upon medullary anemia with subsequent vasomotor regulation. Cushing,[61] in 1902, stated:

> When, however, the local process is in the proximity of, or, if remote, when its effects are so far reaching that the vital centers of the bulb are compromised, the one symptom which with regularity is called forth, and which betokens a serious alteration in the local circulation is a persisting rise in blood pressure, which may or may not be associated with a pronounced vagus pulse, with rhythmic alterations in blood pressure, and with a retardation or periodicities of the respiration approaching a Cheyne-Stokes type.

Up until the last decade considerable dependence was placed upon blood pressure readings in cases of acute craniocerebral injuries. It is now generally accepted, however, that in acute cerebral injuries little dependence should be placed upon the blood pressure findings (Holbrook[9]) and that when blood pressure changes do occur as the result of cerebral compression, considerable damage has already been done to the cerebrum and medullary centers. Blood pressure readings are, of course, invaluable in the diagnosis and in determining the progress in cases of acute craniocerebral injury in which there is an associated shock. Bower[44] found that there is no constant direct relationship between the cerebrospinal fluid pressure and the blood pressure. Holbrook[9] has observed many cases in which there was marked increased intracranial pressure, but in which there was no significant blood pressure change. This is also supported by Stewart's findings in 617 cases of skull fracture. The high average blood pressure in the series was, systolic 140, diastolic 77 mm. of mercury, whereas the low average was, systolic 117 and diastolic 71 mm. of mercury. The unreliability of placing too much dependence on blood pressure findings in the diagnosis of acute craniocerebral injury has recently been emphasized by Gage,[62] Fay[11] considers blood pressure determinations of great importance in acute head injuries. The diastolic pressure which represents the resistance offered the circulating blood is most important. Without sufficient tension (diastolic) there is rapid loss of oxygen, so that the blood reaching the capillary bed contains relatively little of it. As Landis[46] has shown anoxemia increases the permeability of the vessels with a resulting edema. In this way a vicious circle is set up. Fay[11] believes that the diastolic blood pressure must be kept above 40 mm. of mercury. Henschen[21] believes that blood pressure determina-

tions may have a localizing value as he has found that the blood pressure reading on the side of injury is often 20 mm. greater than it is on the uninjured side. Experimentally, Jackson[22] found that the application of pressure over the temporal and parietal regions produced no change in blood pressure, whereas pressure applied to the medulla caused first a slight rise and later a fall in blood pressure.

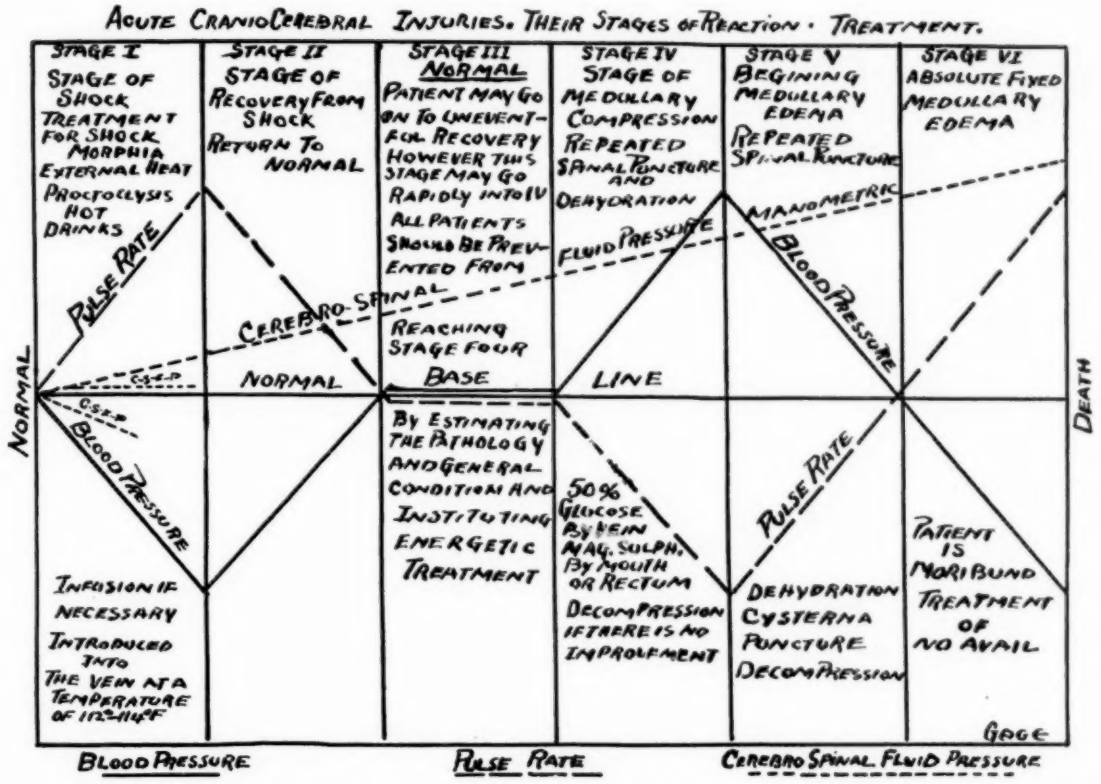
ACUTE CRANIOCEREBRAL INJURIES. THEIR STAGES OF REACTION · TREATMENT.
STAGE I
STAGE OF SHOCK
TREATMENT FOR SHOCK MORPHIA EXTERNAL HEAT PROCTOCLYSIS HOT DRINKS
STAGE II
STAGE OF RECOVERY FROM SHOCK
RETURN TO NORMAL
STAGE III
NORMAL
PATIENT MAY GO ON TO UNEVENTFUL RECOVERY HOWEVER THIS STAGE MAY GO RAPIDLY INTO IV
ALL PATIENTS SHOULD BE PREVENTED FROM REACHING STAGE FOUR
STAGE IV
STAGE OF MEDULLARY COMPRESSION
REPEATED SPINAL PUNCTURE AND DEHYDRATION
STAGE V
BEGINING MEDULLARY EDEMA
REPEATED SPINAL PUNCTURE
STAGE VI
ABSOLUTE FIXED MEDULLARY EDEMA
PULSE RATE
CEREBRO-SPINAL FLUID PRESSURE
MANOMETRIC
BLOOD PRESSURE
NORMAL
BASE LINE
DEATH
C.S.F.
BLOOD PRESSURE
INFUSION IF NECESSARY INTRODUCED INTO THE VEIN AT A TEMPERATURE OF 112-114°F
BY ESTIMATING THE PATHOLOGY AND GENERAL CONDITION AND INSTITUTING ENERGETIC TREATMENT
50% GLUCOSE BY VEIN MAG. SULPH. BY MOUTH OR RECTUM DECOMPRESSION IF THERE IS NO IMPROVEMENT
PULSE RATE
DEHYDRATION CYSTERNA PUNCTURE DECOMPRESSION
PATIENT IS MORIBUND TREATMENT OF NO AVAIL
GAGE
BLOOD PRESSURE
PULSE RATE
CEREBRO SPINAL FLUID PRESSURE

CHART 2. Stages through which patients with acute craniocerebral injuries may pass in those cases in which the lesion is progressive. It is evident that the pulse rate and blood pressure vary considerably with the degree of shock and increase in intracranial pressure. Stage III represents that period after the patient has recovered from shock, at which time pulse rate and blood pressure determinations may be normal, yet in which there may be an increased intracranial pressure. This can be determined only by the determination of cerebrospinal fluid pressure. (After Gage, I. M. AM. J. SURG., 6: 64, 1929.)

THE SPINAL FLUID

Of greatest importance from a diagnostic and prognostic point of view is the determination of the cerebrospinal fluid pressure, as well as the character of the fluid. As the immediate symptoms in acute craniocerebral injuries are the result of increased intracranial pressure, except in those cases where there has been extensive injury of the cerebrum, a knowledge of the cerebrospinal fluid pressure would be of great value as regards diagnosis, prognosis, and treatment (Chart 2). Fay[11] states:

A lumbar puncture with careful manometric pressure readings *must* be done and irrespective of the claims made by those opposed to lumbar puncture, an intelligent management of the case is impossible without knowledge of the pressure mechanism and the presence of bloody spinal fluid, which is frequently encountered where no signs or symptoms may disclose its presence.

Jackson,[22] in 1922, reported his results in 100 cases of acute cranial injuries in which spinal fluid pressure determinations were made and in which spinal tap was used therapeutically. The cerebrospinal fluid pressure was above 30 mm. of mercury in 14 per cent of his cases, the highest reading being 60 mm. In 34 per cent the pressure was between 20 and 30, and in 44 per cent

the pressure varied between 10 and 20 mm. of mercury. Bower,[44] in 1923, reported that lumbar puncture had been used routinely in all cases of craniocerebral injuries at the Samaritan Hospital for a period of seven years and no untoward results had been observed. He emphasized the importance of using a needle with a three-way stopcock in order to prevent an escape of cerebrospinal fluid. In a series of 316 cases admitted to the Boston City Hospital and analyzed by Munro,[63] lumbar puncture was performed and manometric readings of the cerebrospinal fluid pressure were made in 36. In the patients who recovered, the highest pressure recorded was 60, the lowest was 4, and the average 16 mm. of mercury. In 7 fatal cases the highest pressure was 100, the lowest 10, and the average 39 mm. of mercury. Spinal puncture was performed in 414 of McCreery and Berry's[41] 520 cases of cranial fracture. The spinal fluid pressure was increased in 209, normal in 185, decreased in 12, and not noted in 6 of their cases. They believe that spinal puncture is of great diagnostic value. In comparing the differences in cerebrospinal fluid pressure in cases of craniocerebral injuries between the white and colored races, Weaver[40] found that among 300 cases occurring in the white race, there were 190 cases of hypertonicity as compared with 218 cases among 300 occurring in the colored. Connors,[13] Fay,[11] Holbrook,[9] and Symonds[27] believe that a diagnostic lumbar puncture should be made routinely in cases of acute craniocerebral injuries. Newell[5] employs manometric readings of the spinal fluid, but believes that other methods of examination are more important. McClure and Crawford[3] are of the opinion that lumbar puncture should be done only when there is a definite indication. They state that it should be done slowly and cautiously. In their series of 441 cases, lumbar puncture was performed in 148 cases or 33.6 per cent. Forty-seven and three tenths per cent had pressures under 10 mm. of mercury, 39.8 per cent from 11 to 20, 10.8 per cent from 21 to 30, and 2 per cent above 30 mm. of mercury. In Munro's[63] series of cases the comparison of the spinal fluid pressures in the fatal and non-fatal cases reveals that the average intracranial pressure is nearly two and a half times higher in the fatal than in the non-fatal cases. Even though it is desirable to perform a lumbar puncture and determine the cerebrospinal fluid pressure as soon as possible after an acute craniocerebral injury, it is generally accepted by most authors that this procedure should not be performed in the presence of shock. Aside from the fact that patients in shock bear any operative manipulation poorly, lumbar puncture performed at this time is of relatively little diagnostic aid, as even in those cases in which there is extensive cerebral injury, the cerebrospinal fluid pressure is apt to be normal or decreased, because of the decreased arterial and venous pressures.

Aside from the determination of the cerebrospinal fluid pressure, a knowledge of the character of cerebrospinal fluid is of great value as regards prognosis and treatment in craniocerebral injuries. Thirty-nine and nine tenths per cent of the 148 cases in which lumbar puncture was done in McClure and Crawford's[3] series, the spinal fluid was bloody and it was clear in 60.1 per cent. Eighty-three and three tenths per cent of their cases in which death occurred, the spinal fluid was bloody. In Munro's[63] series the spinal fluid contained blood in 57 cases and was clear in 26. In Stewart's[13] series, lumbar puncture was performed in 165 cases, bloody fluid was obtained in 90.5 per cent, and clear fluid in 10.4 per cent. In 47 cases in which lumbar puncture was made in Vance's series of cases, bloody fluid was found in all three tubes in 39. In the 414 cases in which a lumbar puncture was made in McCreery and Berry's[41] series, the fluid was clear in 13, contained blood in 398, and contained pus in 3. The authors believe that blood rarely occurs in the cerebrospinal fluid in traumatic cases unless there is an asso-

ciated cranial fracture. Aside from indicating the severity of the lesion, blood within the cerebrospinal fluid is of importance as far as treatment and subsequent sequelae are concerned. Essick[31] found experimentally that when laked blood was injected into the subarachnoid space, there occurred within six hours a definite sterile meningitis. Bagley[32] was able to demonstrate experimentally that blood injected into the subarachnoid space of dogs produced marked systemic changes. Immediately after the injections the animals became spastic and recovered from the narcosis slowly. In the adult animals there frequently followed convulsive movements and frothing at the mouth. The animals were hypersensitive, irritable, and the nutrition was poor. In puppies the most startling effect was noted, in that there was a diminished activity and a poor development. Late in the course of the meningeal reaction, changes in the cortex were observed. In 6 out of 19 puppies in which blood was injected into the subarachnoid space and on which autopsies were performed, a definite dilatation of the ventricles was found. Fay[34] has described a type of cerebral atrophy caused by collections of fluid in the subarachnoid space, which is a sequel to subarachnoid hemorrhage.

In contrast to the authors already mentioned, there are certain authorities who believe that lumbar puncture is dangerous and should not be performed in cases of craniocerebral injury in which an increased intracranial pressure is suspected. These authorities believe that because of the sudden decrease in the intraspinal pressure, a herniation of the medulla into the foramen magnum may occur. McClure and Crawford[3] believe that lumbar puncture should be done only in selected cases and that the cerebrospinal fluid should be withdrawn slowly and carefully. Henschen[21] is of the opinion that lumbar puncture is dangerous and should never be used in the presence of increased intracranial pressure. Besley[47] believes that lumbar puncture is not free from danger. Sachs[64] is also definitely opposed to lumbar puncture in acute craniocerebral injury.

As a localizing sign Muck[65] has been employing a phenomenon which he observed and reported in 1924. He found that in certain patients with cerebral lesions if the nose were sprayed with a 1:1000 adrenalin solution, following which the nasal mucosa on the anterior end of the anterior turbinate were stroked by means of a smooth probe, that a white line, which persisted from fifteen to thirty minutes, occurred at the point of contact with the probe. Normally, a red line appeared at the point of contact with the probe in the anemic area produced by the adrenalin, all of which disappeared in about fifteen minutes. The white line here described persisted long after the anemia produced by the adrenalin had disappeared. In his original publications Muck[65] stated that this phenomenon occurred in patients with migraine, brain tumors, and in patients with brain injuries. He believes that the reaction is due to a hyperactivity of the sympathetic fibers, resulting in increased irritability of the vasoconstrictors of the nasal mucosa. In subsequent publications Muck[66–69] states that this phenomenon occurred on the side of injury and believes that it is indicative of injury to the pia. In the examination of over 200 cases of craniocerebral injuries, he[67] found that the white line sign was regularly present and almost without exception on the injured side. In 49 left-sided injuries the white line was on the left side in all but 9 and on both sides in one of these 9. Of 38 left-sided parietal injuries the phenomenon was present on the left side in 35, on the right side in 3, on both sides in 11. Of 131 either right or left-sided injuries the phenomenon was present on the contralateral side in only 13. In 1929 Muck[68] reported 92 cases of cerebral injuries examined by this method, and states that if the injury involves either of the hemispheres the phenomenon is present always on the homolateral side. It is not positive

in injuries of the facial bones, injuries of the scalp, and extradural wounds. As the phenomenon is also present in cases with cerebrospinal syphilis, epidemic meningitis, and lethargic encephalitis, it is important that these conditions be excluded when employing the test. Muck's observations have been confirmed by Joel.[70]

ROENTGENOGRAPHY

The relative importance of roentgenography in the diagnosis of craniocerebral injuries is a matter of controversy. It may be stated, however, that all cases of acute craniocerebral injury should have roentgenograms of the skull for two possible reasons: (1) in order to eliminate the possibility of a depressed fracture, a knowledge of which is absolutely essential in order that the correct and proper therapy be instituted; (2) because of the high regard which the laity and the legal profession have for cranial fractures. A failure to obtain a roentgenogram in a suspected cranial lesion, especially in a medico-legal case, would indicate, at least in the eyes of a jury, improper care of the patient. It is obvious that a roentgenogram will show only cranial and not cerebral lesions. It must not be forgotten that aside from depressed fractures, the most important lesion in craniocerebral injuries is not the injury to the cranium but the cerebral lesion. Fay[11] even advocates making no roentgenogram when the patient is first seen, because the plates are usually of little value and if a depressed fracture of such a degree is present ,which will require elevation, it can be recognized at the initial examination. Roentgenograms, also, are not infallible, even in cases of cranial fracture, as illustrated by the following studies: In Stewart's[13] series of 617 cases of cranial fracture only 73.1 per cent of the fractures showed positive roentgenologic evidence of fracture, whereas 26.8 per cent gave negative results. In the latter group 10.7 per cent showed linear fractures at the time of operation and 12.3 per cent were diagnosed as basal fractures by other signs and symptoms. Eleven and six-tenths per cent were found to have basal fractures at post-mortem examination; 2 per cent proved to be fractures of the vault, which were slightly depressed when the wound was explored. Roentgenograms were made in 80.3 per cent of the 441 cases of acute craniocerebral injuries reported by McClure and Crawford.[3] In only 35.9 per cent of the cases in which roentgenograms were made was evidence of fracture obtained; in 10.7 per cent of the clinically positive cases roentgenograms were reported negative, and in 2.8 per cent of the cases there was roentgenologic evidence of fracture in the absence of positive clinical signs. In the 520 cases of cranial fracture reported by McCreery and Berry[41] *x*-ray examinations were made in 220 cases and found negative in 61 per cent. Fractures of the vault were found in 75 of the cases and fracture of the base in only 13.

(*To Be Concluded in June*)

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RADIUM THERAPY OF TUMORS OF THE GENITOURINARY TRACT*

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SOME fifteen or twenty years ago radium was first tried as a therapeutic agent in malignant diseases of the prostate, bladder, penis and testicle. The reason for its trial is obvious. Surgery had proved to be singularly inadequate in attempting to control these diseases. For a good many years surgery had devised and perfected new and elaborate operations in its attempt to cope with them. As a rule, the more elaborate the operations the higher the operative mortality became. Instance total cystectomy with implantation of the ureters into the bowel with a mortality of upwards of 50 per cent. This increasing operative mortality might have been justified if more cases had been cured. This was not the case.

Because it had a definite specific effect upon cancerous tissue, radium was suggested as a substitute for surgery. After fifteen years of work at the Memorial Hospital, work in which successes mingled with failures, it seems that today the original faith that radium might prove of value in controlling cancer has been more than just fied.

Let me here interject that radium treatment of any malignant disease is becoming more and more a problem that can best be dealt with in especially equipped hospitals. Radium is expensive. Its proper use implies a certain amount of special training. Many of the failures of radiation therapy are due to the fact that sufficient amounts of radium are not at hand when any particular case is dealt with. The effect is the same as if a surgeon sliced off a small part of a tumor, rather than removed it in its entirety.

And just one word about radium burns. It is impossible to eradicate a tumor without causing some radium effect upon the surrounding tissues. This is the so-called and much feared radium burn. My point of view for a great many years has been that I fear the cancer much more than the radium burn. The one causes death. The other is a transient affair.

Let us see how radium therapy has affected the treatment, the prognosis and our general conception of the control of 4 genitourinary carcinoma: cancer of the penis, teratoma of the testicle, cancer of the prostate and cancer of the bladder.

CARCINOMA OF THE PENIS

The older conception of the cure of carcinoma of the penis did not distinguish at all between the different forms and different locations of the carcinoma, and it was believed that all cases should be treated with amputation of the penis at the triangular ligament, with implantation of the urethra in the perineum, and at the same time bilateral dissection of the glands of both inguinal regions. A careful study of these cases has revealed the following facts: That the carcinoma may be papillary in type, and may be entirely confined to the foreskin, or it may be entirely confined to the glans penis, or it may be a combination of these two; that it may be of the infiltrating type, growing into the substance of the penis, penetrating Buck's fascia, and so growing up along the copora cavernosa; that involvement of the inguinal glands by the carcinoma is rare; that infection of the inguinal glands without cancerous involvement is quite common; that when the inguinal glands are both cancerous and infected routine dissection has little or no chance of controlling the cancer. Therefore, our therapy at present is as follows: The foreskin must be freed either by dorsal slit or by circumcision, so elimi-

* Read at the St. Louis Clinics June, 1930. From the Dept. of Urology, Memorial Hospital, N. Y.

nating the causative factor of carcinoma, the irritating secretion. In 3 recent consecutive cases, the carcinoma was entirely confined to the foreskin, and simple circumcision eliminated the carcinoma. All of these patients are well five years after. Two had no further therapy. The third had a recurrence which necessitated amputation of 1 in. of the penis. He is well five years after.

When the carcinoma is papillary in type, or if infiltrating and if Buck's fascia has been penetrated but a slight distance, then operation may be entirely eliminated, and the carcinoma controlled by radium, as a rule applied on the surface.

We are seeking to further extend the field of radium in the infiltrating type, and while formerly we believed that few could be controlled in this way, we are now applying it to more cases with deeper infiltration. On the other hand if the infiltration is extensive then we excise the penis 2 cm. beyond the growth. The excised portion is dissected at the operating table to determine accurately if we are beyond the growth. No routine inguinal dissection is done. The infection of the inguinal glands is eliminated by its control at the source, the penis. The inguinal glands are treated by a combination of deep *x*-ray therapy and radium pack, with implantation of radium in any suspicious glands.

If the primary lesion is confined to the foreskin it is removed by circumcision, and any suspicious areas remaining are irradiated. If the primary lesion is 2 cm. or less in diameter, superficial, and metastases cannot be detected, external irradiation alone is used. The tumor is treated with a radium plaque,* the dose being 1200 mc. hours per square centimeter, at 1 cm. distance.

There were 13 patients in this group. Twelve, or 92 per cent, are living, without signs of disease. One patient died at another hospital following an operation. One of these men lived from twelve to eighteen months; 3 from eighteen to twenty-four months; 1, from two to three years; 2, from three to four years; 2, from four to five years; 2, from seven to eight years and 1, for nine years four months after the first irradiation.

Occasionally, the carcinoma, though small, has penetrated deeply into the cavernous tissues. Frequently, undermining has gone so far that the deeper parts of the tumor are relatively inaccessible to intense external irradiation. In such cases irradiation with the plaque is followed by a conservative amputation.† Four patients were so treated. All of them are living and well; 1, from two to three years; 2, from four to five years and 1, from six to seven years after the first irradiation.

If the primary tumor is larger than 2 cm. in diameter and metastases are not found, the treatment of choice is usually irradiation with the plaque followed in from three to four weeks by a conservative amputation. On those patients who present extensive tumors which have already destroyed a considerable proportion of the penis, a similar amputation is performed without preoperative irradiation.

In this group there were 31 patients. Nineteen, or 61 per cent, are living and well; 5, or 16 per cent, are known to be dead, while 7, or 22 per cent, are lost from the records and are classified as dead. The living have survived: 1, from eighteen to twenty-four months; 4, from two to three years; 2, from three to four years; 4, from four to five years; 3, from five to six years; 4, from seven to eight years and 1, from eight to nine years after the first irradiation.

Eighteen patients were first seen with both a primary lesion and metastases. Three, or 16 per cent, are living, 2 with signs of disease; 15, or 82 per cent, are dead.

* The plaque is a box 1 cm. square which contains radium emanation enclosed in silver capsules, the walls of which are 0.5 mm. thick. The side of the box which overlies the tumor is made of brass, 1 mm. in thickness.

† Conservative operation is believed to be a distinct advance in rational therapy. Amputation is performed 2 cm. proximal to visible or palpable evidence of disease. The success of the measure depends on the knowledge that metastasis is by embolism. It is not at all uncommon to preserve so much of the organ that coitus is possible.

Therefore, of 66 patients, 36, or 57.5 per cent are alive, and as far as can be determined, free of disease. *And more, there has been no operative mortality.*

TERATOMA OF THE TESTIS

In no tumor has radiation produced more brilliant results than in this disease. The pathology of the disease is that the teratoma starts in the rete testis, then grows either toward the testicle or epididymis, or both. Then it metastasizes by way of the veins or lymphatics, or both. Metastases form along the course of the spermatic vessels.

This has suggested to many (Hinman and others) that the cure was to remove the testicle, and by extensive dissection of the retroperitoneal glands, to eliminate all of the carcinoma.

This has never appealed to me as a feasible way to control retroperitoneal metastasis.

Our course of procedure is as follows: In the primary cases, in which no surgery has been done, the testicle is thoroughly irradiated with the radium pack. The course of the spermatic vessels on the side affected is also thoroughly radiated by radium pack or deep *x*-ray therapy. The only operation that is done is the removal of the testicle under local anesthesia. The cord is cut first, and the testicle is removed from its bed afterward, care being taken not to squeeze the testicle, and so preventing the dissemination of the cancer. This operation is done about two months after the first radiation, and has no mortality.

At the time this article is written we are able to present data on 113 patients treated and followed in this hospital. Of these 113 cases, 41 are living and clinically free from disease. The table indicates the time duration:

9 –12 months	1	4– 5 years	3
1 –1.5 years	5	5– 6 years	3
1.5– 2 years	9	6– 7 years	2
2 –2.5 years	6	7– 8 years	0
2.5– 3 years	2	8– 9 years	2
3 – 4 years	6	9–10 years	1
		10 years	1

The following case report is of interest.

The patient was a negro chauffeur, aged thirty-seven years. He was admitted to the hospital in May, 1925, with a history of painless swelling of the right testis over a period of five months. The testis steadily increased in size and two weeks before admission first became painful. Three months prior to entering the hospital the patient began to cough and had frequent night sweats. He had lost 36 lb. in weight. Examination revealed a tumor of the right testis measuring 14 cm. in circumference. A mass 5 × 7 cm. was palpated in the right abdomen and *x*-rays of the chest showed extensive pulmonary metastases. In addition there was a hard supraclavicular node measuring 1 × 2 cm. No operation was done. The patient was treated with a great deal of high voltage *x*-ray and with radium. The testis was reduced to a firm fibrotic mass. The metastases disappeared and the patient is now clinically well and free from demonstrable disease for four and a half years from the time treatment was first instituted. The skin shows practically no effect from the treatment.

CARCINOMA OF THE PROSTATE

Carcinoma of the prostate still holds its place as the great urological puzzle. We know next to nothing as to its cause. We have no real, practical method in general use to make the diagnosis of this condition sufficiently early to give any sort of treatment a fair chance of success. If we by hazard make an early diagnosis of carcinoma of the prostate we are thoroughly in a muddle as to the best way to control this carcinoma. This paper is written in an attempt to analyze the reasons for our failures in the past and with a look toward the future.

We have found that in but between 2 to 5 per cent of all cases seen at the Memorial Hospital is the carcinoma confined to the prostate. Young reports 27 radical operations for carcinoma of the prostate, the first in 1904 and the last in 1927,[1] just a little over one a year. This would seem to indicate how very few cases come to his service which he believes are appropriate

[1] Lewis, D. Practice of Surgery. Vol. 9, Chap. 21, p. 94.

for radical operation. Wildbolz operated upon 40 out of 145 patients with prostatic carcinoma.[2]

It seems superfluous to say that earlier diagnosis is of prime importance, and earlier diagnosis by means of pathological examination. A method for obtaining a specimen from the suspected prostate has been perfected by one of our staff. This is done with a simple aspirating needle, and it is effective in 66 per cent of cases. A discussion of the various methods to control prostatic carcinoma after an early diagnosis has been made reveals the fact that no two urologists seem to be in accord as to the best way to accomplish this.

A review of the use of radium in carcinoma of the prostate at the Memorial Hospital has revealed the following interesting facts: From October, 1915 to January, 1917, we saw 46 cases of prostatic carcinoma at the Memorial Hospital. In but one of these cases was the carcinoma confined to the prostate. Five of the 46 patients lived more than five years. None of these 5 cases, as far as we could see, had any gross evidence of active carcinoma. These cases were treated by the insertion of steel radium-bearing needles through the perineum into the prostate and seminal vesicles, giving small doses, 200 or 300 mc. hours for each needle, and then repeating this dose every two or three months until the condition was controlled or not. In this way we were certainly able to cure some cases, as we have had the autopsy of one patient who died seven years after first seen; the diagnosis of carcinoma was made from the prostate removed before operation, and the autopsy showed no carcinoma anywhere.

Since that first series we have not done as well. We have been in a transition state, changing to gold seeds and have pretty thoroughly come to the conclusion that gold seeds cannot be implanted through the perineum into the prostate with any great degree of accuracy. We believe that in most cases of prostatic carcinoma a much larger dose of radium than heretofore used is necessary to control the disease; in other words, doses comparable to those we have used in controlling bladder carcinoma.

A certain percentage of prostatic carcinoma are highly malignant and radiosensitive. Because of this I believe that all cases of prostatic carcinoma, before anything is done, should be subjected to a thorough cycle of deep *x*-ray radiation, using five portals of entry. This at best gives only about 1½ erythema doses to the prostate, whereas we believe that somewhere between 10 and 15 erythema doses are necessary to control the large majority of prostatic carcinoma. Because of the necessity for a large dose of radium accurately placed within the prostate I have quite reversed my original contention that the best method was through the perineum. I believe that cystotomy should be done, any obstructive portions of the prostate removed with cutting forceps or a cautery, and the entire tumor, periprostate, periprostatic region and seminal vesicles, if they are involved, implanted with radium seeds, using seeds of 2 mc. each to every centimeter of tumor. It seems to me that the suprapubic exposure is better for this purpose than the perineal one, because the seeds can be more accurately placed and because the prostatic region is not dissected up, so reducing its value as a productive barrier to the radium seeds.

The mortality of this operation is not so great as that of Young's radical removal, and while it is not a beautiful piece of technique, I believe it will prove in the long run a much more effective method to control prostatic carcinoma, one that can be used by many more urologists. It will certainly offer a sure way of controlling the bladder invasion of the carcinoma which so frequently occurs in the glands of Albarran and the bladder base.

CANCER OF THE BLADDER

The treatment of bladder tumors is still

[2] Wildbolz, H. Die Erfolge operativer Therapie des Prostatskarzinoms. *Schweiz. med. Wchnschr.*, 58: 726, 1928.

in a state of evolution. Surgery and radium have been and still continue to be contestants for honors.

A comparison between the results of the radium implantation and operative removal of bladder cancer is difficult because surgery picks the cases which are operable and discards the rest.

At the Memorial Hospital we have subjected to radiation every patient with bladder cancer in whom the cancer was believed to be confined to the bladder, no matter how large the tumor was. Therefore, in this series are included many inoperable cases. In a fair percentage of cases the tumor occupied one-third or more of the bladder. In these cases 28 per cent were tumors whose bases were 6 sq. cm. or under.

TABLE 1

PAPILLARY CARCINOMA

Diagnosis, Clinical

(Papilloma with atypical cells are grouped under this heading)

Cases: 45
Clinical and pathological diagnosis agree—36
Clinical and pathological diagnosis disagree—9
Controlled: 30 cases—66 per cent
Controlled over three years: 25 cases—55.5 per cent

1	1–2	2–3	3–4	4–5	5–6	6–7
1	3	0	2	6	3	3

7–8	8–9	9–10	10–11	11–12	12–13
2	2	5	1	0	1

Not controlled: 15 cases—33 per cent

INFILTRATING CARCINOMA

Diagnosis, Clinical

Cases: 82
Clinical and pathological diagnosis agree—47
Clinical and pathological diagnosis disagree—35
Controlled: 30 cases—36.5 per cent
Controlled over three years: 23 cases—27.8 per cent

1	1–2	2–3	3–4	4–5	5–6	6–7
3	2	2	4	3	3	4

7–8	8–9	9–10	10–11	11–12	12–13	13–14
3	2	3	....	.....	.....	1

Not controlled: 52 cases—63.5 per cent

In 72 per cent the cases were greater than 6 sq. cm.

The Location of the Tumor: In 127 tumors 81, or 63 per cent, touched or were adjacent to the trigone. Many of these would have required total cystotomy if operative removal had been contemplated.

In 19, or 15 per cent, the location was on the base posterior to the trigone. In 18, or 14 per cent, the tumor was on the lateral walls and easily removable.

In 1, or 7 per cent, it was on the apex. In 8 the site was not designated.

In the 63 per cent of tumors touching the trigone the operative mortality following the surgical removal of these tumors, if that were possible, would have been between 10 per cent and 20 per cent, and a fair number of these tumors could not have been removed surgically.

DIFFERENT FORMS OF RADIATION

We have been able from the very start (1914), to control a good percentage of malignant bladder tumors with radium. We first used screened radium applied in a somewhat hit or miss manner. Then partly screened and partly unscreened (glass seeds), more accurately applied, but with much caustic beta radiation. And finally accurately applied gold seeds giving off no beta radiation.

Beta radiation certainly causes sloughy anus of the bladder, which only too often becomes covered with troublesome phosphatic deposits. On the other hand two of the most malignant tumors we have ever controlled were controlled solely by glass seeds.

It is an open question at present whether or not this caustic action of beta radiation is a factor in controlling bladder cancer.

The size of the dose of radium is an important factor. The reason why many who use radium fail is that a very small dose is used. I have analyzed a good many such cases and have found almost without exception this to be the reason for failure.

One gold seed of 2 mc. hours to 1½ sq. cm. of tumor is a *minimum dose*. I have

put as many as 40 such seeds in a single very large tumor. Considerable bladder irritability and some rectal irritation may follow this dosage (if the seeds be near the rectum), and the so-called radium burns may follow this administration.

I have always worried more about the malignancy of a bladder tumor than over a radium burn. We have calculated that about ten times an erythema dose is necessary to control the radioresistant tumors. This accounts for the reason that deep *x*-ray therapy so often fails. It is difficult to get into the tumor by this means much more than 1½ erythema doses.

THE SUPRAPUBIC OPERATION

Finally, let me stress the decided difference between the operative mortality when a tumor is removed by surgery and when it is implanted by radium by the suprapubic route. In 109 consecutive personal cases of the suprapubic implantation of radium 4 patients died in the hospital, an operative mortality of 3.6 per cent. One died of shock and hemorrhage, notwithstanding two blood transfusions, 1 of diabetic coma, 1 of uremia, 1 of shock; a poor heart and old age contributed.

A considerable number of these cases would have been classed as inoperable.

Operative removal in these cases of this series which were operable would have been between 10 per cent and 20 per cent.

In doing the suprapubic implantation spinal anesthesia should be used, the bladder should not be mobilized; the abdominal wound should be thoroughly screened with gauze before opening the bladder; great care should be taken not to spill the bladder contents over the wound; a good exposure of the tumor is necessary; the Cameron light should be used for retraction and to illuminate the bladder; open wire retractors devised by us at the Memorial Hospital are very useful for a good exposure of the tumor; the papillary portions of a tumor should be removed by some form of cautery; the radium implantation should be very accurate; a small suprapubic drainage tube (18 to 22° F.) should be left in place for about a week or longer, if the bladder is dirty or the radium dose is very large; the bladder is not sutured to the abdominal wall.

ALLERGY AS A CAUSE OF GASTROINTESTINAL DISORDER*

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ALLERGY is important in its relationship to the gastrointestinal tract not only because it can produce serious gastrointestinal disorder, but also because it can simulate both functional and organic disease due to other causes. Consequently, unless recognized, it can lead to gross error in diagnosis. It is important also because the gastrointestinal turmoil caused by allergy can actually precipitate organic disease which may require surgery for relief. It is important, finally, because therapeutic measures for the relief of gastrointestinal allergy are sensationally effective if adequately administered.

Allergy can involve almost every active tissue. It is characterized by certain features which make its recognition relatively simple and certain. A physician can diagnose the condition correctly, as a rule, if he is well acquainted with the subject. Allergy can simulate a large variety of diseases but rarely simulates any of them perfectly. It should be looked for whenever the symptoms displayed by a patient do not fit well with known disease patterns.

The typical local lesion of allergy is characterized by anemia, and eosinophilic infiltration of the part directly affected and a surrounding area of erythema. Typically, this constitutes a hive. It is associated usually with sensory disturbance such as itching and, in the gastric tissues, sometimes by pain. In addition to this, there is a disorder which occurs as part of a general reaction of allergy. This consists basically of over-activity of one or more or all of the branches of the vagus system. It causes anomaly in muscle contraction and in secretion. In the case of widespread allergy, shock may result characterized by disappearance of pulse and respiration, cyanosis, and loss of consciousness. Shock may terminate fatally unless promptly and adequately treated. It is interesting to relate that each of these phases of allergy can be almost immediately relieved within a matter of moments through prompt and adequate use of adrenalin.

Allergy may make its appearance at any point in the gastrointestinal tract from the lips to the rectum, giving rise to the signs of local and general reaction as previously mentioned. It can cause symptoms which may be mild or severe, acute or chronic, intermittent or continuous. The extreme symptoms which are occasionally observed are often alarming. Nausea, vomiting, and diarrhea may equal that caused by any other disease known to medical science. Infiltration of the tissues with edema may cause complete obstruction and finally, pain may equal that caused by gallstone, kidney stone, or gastric crisis. Allergic disorders characterized by anemia and edema of the membranes, increased tone of non-striated muscle and increased secretion, can easily precipitate inflammatory disease in the gastrointestinal tract or its appendages. I have observed a number of cases of acute appendicitis which commenced with an attack of alimentary allergy. I believe the characteristic symptom of acute appendicitis as mentioned in the common textbooks, that is, pain in the epigastrium followed after a day or so by pain and tenderness in the region of the appendix, is frequently caused primarily by gastric allergy which is later followed by a complicating inflammatory disease of the appendix itself.

It was mentioned before that alimentary allergy can simulate many functional and organic diseases but that it rarely simu-

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lates any of them perfectly and can almost always be distinguished from the other diseases. It can be suspected whenever alimentary symptoms do not fit well with the usual symptomatology of other known diseases and especially if the disturbance is associated with other easily recognized symptoms of allergy such as allergic coryza; swelling and itching of the pharynx; hoarseness and edema of the larynx; bronchial cough or asthma; or by skin manifestations such as pruritis, urticaria, angioneurotic edema, or eczema. The condition may also be suspected in the absence of these easily recognized symptoms if a well marked family history of allergic disease can be obtained, or if the condition disappears after a therapeutic test with adrenalin. The severest symptoms of allergy should yield to adrenalin unless complicated by some non-allergic change in the affected tissues. Adrenalin must be administered with precision. Unfortunately, we have no way of determining the ideal dose for a given patient or even for the same patient at different times. It is a good rule, therefore, to give about $\frac{1}{10}$ c.c. or a little more at five-minute intervals until tremor appears. Tremor usually indicates that the administration has been adequate and that true allergic symptoms should soon subside. If the dose is pushed to the point of causing cardiac arrythmia or heart pound, a rubber tourniquet should be placed around the arm above the site of inoculation and released at frequent intervals. An excessive adrenalin effect can be stopped promptly in this way (Insley).

Symptoms of alimentary reaction can be divided into two distinct groups: first, those which occur as a result of direct contact between the tissues and the offending agent and, second, those which occur as part of a general reaction caused by contact with a substance after absorption. As an illustration of the former type may be mentioned the violent gastrointestinal symptoms which occur as a result of the ingestion of a small amount of honey in honey-sensitive cases. Pain, nausea and vomiting occur as a rule within a few minutes of the time of ingestion of the honey and may be shortly followed by symptoms of general reaction. I have observed a case in which the ingestion of honey on two occasions caused gastrointestinal symptoms, immediately followed by a convulsion, coma, complete disappearance of pulse and respiration and cyanosis. The application of honey to the skin in cases of this sort gives rise immediately to a typical hive. This type of case reacts in the same way that pollen-sensitive cases react to the application of pollen.

The second type of reaction (alimentary symptoms occurring as part of a general reaction) is observed typically in the case of alimentary symptoms which may follow an insect bite in hypersensitive persons. Here symptoms such as nausea, vomiting, bloating, diarrhea and collapse may be very severe and may actually, in rare instances, cause dehydration, collapse, and death.

Both these types of reaction may occur simultaneously. This is illustrated in pork-sensitive cases. Here a person may have coryza and headache and gastric disturbance caused by direct contact between the membranes and emanations from the food as it is eaten, and later may have urticaria and other general symptoms occurring as part of a general reaction.

The commonest single cause of alimentary reaction is food sensitiveness. Alimentary reaction caused by sensitiveness to drugs, sera, insects, and animal parasites (including intestinal worms) is less common. Finally, as will be discussed subsequently, symptoms caused by sensitiveness to the effect of heat and effort and to the effect of cold are frequent but less common. Pollen, epidermal substances, dust, smoke and volatile oils which commonly cause nasal and bronchial symptoms are rarely absorbed in quantities sufficient to produce reactions in the alimentary tract.

Reactions to foods are interesting. Symp-

toms which are inclined to be chronic and continuous are almost always caused by a food which is eaten repeatedly. Attacks which occur at rare intervals are usually caused by foods which are rarely eaten. It is much easier to make a diagnosis in the latter case because the patient, as a rule, can notice a relationship between cause and effect. In the case of sensitiveness to foods commonly eaten, such as milk, eggs, and pork, the diagnosis is beset with difficulties, especially if the patient is highly sensitive and reacts to traces of the offensive agent. Infants highly sensitive to egg can actually be made ill by the quantity of egg they receive from the lips of a person who has recently eaten egg. Adults highly sensitive to egg can actually obtain enough egg from the eating of hen meat to be made profoundly ill. I have had two individuals highly sensitive to pork who could be made profoundly ill by the trace of lard contained in a small slice of bread. Also one individual who was so highly sensitive to cane sugar that an illness could be produced by placing one or two granules of sugar on the tongue. Several honey-sensitive patients who were not sensitive to the gross constituents of honey such as sugar, were made ill by the trace of foreign substance contained in one drop of honey. One ragweed-sensitive patient who could tolerate commercial honey of five varieties was made ill by a small quantity of wild honey. This may have been caused by its content of pollen.

Whereas a few individuals are highly sensitive, such as those already mentioned, many patients are slightly sensitive and are made ill only by the eating of definite quantities of the offending agent. This is particularly true in children. Many individuals are brought to a state of invalidism through the eating of normal amounts of milk and eggs and can be completely relieved by their partial avoidance.

There is a type of reaction similar in every sense to the allergy as here described caused by specific sensitiveness to the action of physical agents. I have grouped these cases together under the term "physical allergy," meaning altered reactability to the effect of physical agents such as light, heat, cold, and scratches and in the case of heat sensitiveness, to the effect of mental and physical effort). So far as the alimentary tract is concerned, the only reactions to physical agents which are important are those caused by sensitiveness to heat and cold and to the effect of effort. Cases of physical allergy can be divided into two groups of patients: first, those in whom reactions occur only at the point of contact between the tissues and the physical agent and those in whom reactions occur not only at the point of contact but in distant structures as well; in fact, frequently in distant structures only.

Reactions to heat and cold which occur only at the point of contact with heat or cold are rare and in my experience are rarely caused by cold and have but once been caused by heat. Reflex-like reactions, however, that is, reactions which occur in points distant from the point of exposure, are quite common and rather frequently involve the gastrointestinal tract. They can cause gastrointestinal symptoms which may be more or less violent, symptoms such as nausea, vomiting, diarrhea, and pain. Attacks may be associated with other symptoms of physical allergy such as prostration, tremor, headache, allergic coryza, asthma, pruritis, urticaria, angioneurotic edema, and, occasionally, shock.

Heat reactions of this sort may occur as a result of gross exposure to heat in patients who are slightly sensitive, and as a result of almost infinitesimal exposure to heat in patients who are highly sensitive. In the latter case, as small a quantity of heat as is encountered in the drinking of a cup of coffee with a meal may precipitate an attack, or the physical effort of getting up out of a chair may precipitate an attack, or the mental effort of an interesting business deal, or the watching of an athletic contest, or an emotional disturbance may precipitate an attack. In a

fashionable woman who was highly sensitive to heat, a vivacious social conversation was likely to be interrupted by acute diarrhea.

The symptoms in patients who are heat or effort sensitive can be reproduced objectively by the application of heat to the skin. In this way, a diagnosis can be proved. The symptoms can be relieved almost immediately by the application of cold to the skin. Interesting to relate, the symptoms can be produced by heating an extremity such as the arm with a hot lamp even though a tourniquet is applied above the point of application so tightly as to stop the circulation of blood. Evidently the symptoms produced in this case are produced through the sense of heat. Interesting to relate also is the fact that an attack generated in this way can be promptly stopped by the application of cold to another extremity even though a tourniquet be applied above the site of application of cold. A patient who is inclined to have symptoms of this sort can frequently relieve himself by as simple a procedure as holding a piece of ice in his hands or immersing his hands and forearms in cold water. The relief which can be obtained frequently in this way in severe cases is nothing short of miraculous.

In the case of cold sensitiveness, we have a reverse status, that is, symptoms such as abdominal pain, nausea, vomiting and diarrhea often associated with other allergic symptoms such as prostration, tremor, urticaria, pruritis, asthma, allergic coryza, etc., caused directly by the effect of cold on the skin or mucous membranes. A cold drink, a cold food, or the effect of cold on the skin may have like effect. Symptoms in this case can be relieved by the effect of heat or effort. Symptoms such as these can be reproduced objectively by the application of cold and can be relieved objectively by the application of heat in another area. It is surprising to note that the symptoms can be reproduced not only by the application of cold to the skin, but also by the application of cold to an extremity even though a tourniquet be applied above the site of application in such a way as to obstruct the circulation. Likewise, relief can be obtained when produced in this way by heat applied to an extremity distal to a tourniquet which completely obstructs the circulation.

Violent gastrointestinal symptoms, therefore, can be caused by an agent of such minor importance as a sense of heat or a sense of cold, and can be relieved by the opposite sense.

The cases just described are quite different from the so-called contact group of cases of physical effects referred to previously. In the contact case of reaction, the reaction occurs only at the site of contact with the agent unless the application is so gross as to cause a general reaction. I have observed 2 patients who showed marked sensitiveness to cold who would have marked swelling of the lips, esophagus, and abdominal pain, nausea and vomiting after the ingestion of a cold drink or a cold food. In this case the effect of cold upon the skin was negative so far as the alimentary tract was concerned.

Much more can be gained in the diagnosis of gastrointestinal allergy through the agency of family history, past history, physical examination, tests with heat and cold, therapeutic tests with adrenalin and food elimination tests, than through the use of the skin tests ordinarily employed in allergic studies. These facts have been particularly emphasized recently by Rowe who has written extensively and accurately on this subject. Unfortunately skin tests in food cases are very frequently flatly negative.

Brilliant therapeutic results can be obtained in alimentary allergy through the agency of elimination diets; specific treatment in the case of sensitiveness to common foods (such as milk, eggs, or pork) which are difficult to avoid; and through the use of symptomatic remedies, especially adrenalin, ephedrine, atropine, and the salicylates. In the case of physical

allergy, much can be gained through avoidance of undue exposure to the physical agent which causes reaction and through the agency of increasing a patient's tolerance by repeated gradually increasing exposure to the agent responsible for the illness.

SUMMARY AND CONCLUSION

Allergy is important in relation to the gastrointestinal tract in that disturbances caused by allergy can simulate organic and functional disease due to other causes and also through causing edema of the tissues, muscle contraction, and anomalies in secretion, can actually precipitate organic disease.

Allergy in the gastrointestinal tract is more commonly caused by foods than by drugs, sera, insects, and parasites. A reaction similar in every sense to those caused by foods or other material agents can be caused by sensitiveness to the effect of heat and effort or to the effect of cold. Pollen, epidermal substances, dust, smoke, volatile oils, etc., which commonly cause nasal and bronchial symptoms are rarely absorbed in sufficient quantities to produce reaction in the gastrointestinal tract.

The diagnosis of gastrointestinal allergy can be made with relative certainty.

Treatment of the condition is likely to be brilliantly successful if correctly diagnosed.

MANAGEMENT OF GASTRIC AND DUODENAL ULCER

WITH SPECIAL REFERENCE TO INDICATIONS FOR MEDICAL AND SURGICAL TREATMENT*

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ONE of the greatest problems in the treatment of gastric or duodenal ulcer is to determine whether medical or surgical treatment is indicated.

If I had an ulcer of the stomach of not too long standing and there were no surgical complications, such as perforation, pyloric obstruction or repeated hemorrhages, I should certainly elect medical treatment. With rest and the Sippy regimen, the chances of ultimate recovery would probably be from 80 to 90 per cent in my favor.

On the other hand, if there were repeated hemorrhages or the evidence showed location of the ulcer in the duodenum, it would be time to consider a gastroenterostomy. If persistent pyloric obstruction developed, this operation would certainly be indicated. And, if symptoms recurred on slight provocation after correct medical treatment, it would again be time to consult the surgeon.

These factors are but a few of the many intricacies that make peptic ulcer one of the most difficult diseases to treat satisfactorily and justify a reconsideration of the whole subject.

LOCATION OF PEPTIC ULCERS

For practical purposes of diagnosis and therapy, gastric, duodenal and gastrojejunal, or marginal, ulcers may be classed together. Their symptoms and modes of treatment are so nearly similar that we may think of them under the term "peptic ulcers."

It is seldom that ulcers are found exactly at the pylorus. Gastric ulcers are usually located 2 in. or more from the pylorus, while duodenal ulcers as a rule occur ½ in. or more from the dividing point between the stomach and duodenum. Jejunal ulcers, also termed marginal or gastroenterostomy ulcers, appear along the stoma produced by gastroenterostomy.

As to duration, peptic ulcers may be classed as acute, subacute or chronic. They may be simple, perforating or indurated. Multiple ulceration may occur.

INCIDENCE OF OCCURRENCE

In frequency of occurrence, it has been estimated that from 60 to 80 per cent of peptic ulcers are duodenal, with the greater incidence in the male sex. In women the duodenum has a more transverse position, permitting better neutralization of the chyme by the bile and pancreatic juice. In the female, ulceration is more frequent between the ages of twenty and thirty, while in men the more common age of occurrence is between thirty and fifty. Men suffer more frequently from chronic, indurated and perforating ulcers than do women. Jejunal ulceration follows from 2 to 10 per cent of gastroenterostomies. Rarely, have cases of ulceration in infants, as well as in aged people, been observed.

ETIOLOGY

While various theories have been advanced regarding the causative factors giving rise to peptic ulcer, laboratory experimentation has so far failed to support the conjectures of any one group of investigators. That gastric juice has the property of digesting weakened tissue is acknowledged by all investigators. This factor leads one to the conclusion that ulceration may take place from gastric juice erosion when the mucosa has been devitalized as in anemia, nervous strain and worry. There are likewise pathologists

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who are of the opinion that devitalization of tissue may arise from wrong eating and irritation from alcohol and tobacco. Traumatism is sometimes causative. It is possible also that certain individuals have a constitutional deficiency which predisposes them to ulceration.

Other investigators are of the conviction that ulcer of the stomach or duodenum is due to infection from other parts of the body. Such a one is Macrae, of England, who goes so far as to maintain that all peptic ulcers are of infective origin. In my opinion, this has not been proved, though local infection may undoubtedly be considered an etiological factor. It would not appear good judgment to allow an ulcer patient to continue swallowing pus from pyorrhea pockets; but treatment of the focal infection should be considered in the nature of a prophylactic provision, rather than presumptive therapy for cure of the ulcer. Specifically, peptic ulcer may be syphilitic, tuberculous, or of actinomycotic, typhoid or anthrax origin. Occlusion of a blood vessel of the stomach or intestinal wall, as in arteriosclerosis, may give rise to ulceration. Focal infection of the tonsils, teeth, appendix or gall bladder may be considered a predisposing condition, as well as hyperacidity resulting from stricture of the pylorus.

The relationship of peptic ulcer to malignancy is likewise a question upon which there is still much divergence of opinion, with claims varying from 5 to 70 per cent of cases for chronic ulceration as causative of gastric carcinoma.

DIAGNOSTIC PROCEDURE

Peptic ulcer is not always easy to diagnose because of the variability of accompanying dyspeptic symptoms. However, the use of roentgenography is exceedingly valuable for accurate diagnosis. The positive findings of roentgenography show a barium-filled or bismuth-filled crater at the site of the ulcer. A persistent indentation in the outer curve of the gastric wall, opposite to and pointing toward the crater, is a positive sign. The indentation is due to peristaltic spasm and it resists belladonna. In the stomach, the indentation may give rise to the picture known as hour-glass stomach, in which the organ appears to be composed of two chambers, which do not disappear with manipulation or use of belladonna. In chronic perforated ulcer, the roentgenogram shows an accessory, outlying pocket filled with barium or gas. Less definite roentgenographic indications are a suspicious area coinciding with a tender spot, deformity of the first portion of the duodenum, adhesions adjacent to the stomach and extreme spasticity.

A general symptom of peptic ulcer is chronic gastric disturbance of several years' duration, the attacks occurring periodically and lasting from two to six weeks. The attacks do not incapacitate the patient for work, the appetite is normal and undernourishment is not present. Epigastric pain and tenderness are present, but the pain is seldom severe and piercing.

The rhythmic appearance of the pain after a meal may serve to distinguish between stomach and duodenal ulcer. In stomach ulcer the pain occurs in the following rhythm: food-intake, period of ease, pain, then a period of ease before the next meal. The pain occurs one-quarter to two and one-half hours after meals. In duodenal ulcer, the pain, after it starts, continues until the next meal; and the rhythm of occurrence may be indicated in the following order: food-intake, period of ease, then pain until it is relieved by further food-intake. The pain usually occurs in from two to four hours after eating. Thus in duodenal ulcer one might expect occurrence of pain about eleven in the morning, four in the afternoon and in the middle of the night. The patient may be in the habit of keeping a bite to eat by his bedside for relief of the nocturnal pain.

Other general symptoms of peptic ulcer are vomiting, which may give incomplete relief from the gastric pain, and hematemesis. The presence of occult blood in the

feces or in gastric washings is strongly indicative of ulceration. Diagnosis may be furthered mechanically by the various test meals, which in ulcer usually show prolonged digestion and an excess of free and combined acid, though in a very small percentage of cases hypoacidity may be present.

PROGNOSIS AND DIAGNOSIS OF COMPLICATIONS

The complications most to be feared from peptic ulceration are severe hemorrhage and perforation. Duodenal hemorrhage is more dangerous then gastric hemorrhage, but is seldom fatal. It may be so severe as to cause the patient to faint, and is usually followed after twelve or more hours by offensive, tarry bowel movements. Rupture may be classified as acute perforation with diffuse peritonitis, subacute perforation with recurring localized peritonitis, and chronic perforation with localized peritonitis and adhesions.

Uncomplicated peptic ulcer is not accompanied by acute pain. With or without a history of ulcer, sudden excruciating pain so violent as to cause shock and require opiates is indicative of acute ulcerous rupture. It is accompanied by extreme rigidity of the muscles of the anterior abdominal wall, tenderness, and tenseness of the whole body to avoid pain. The patient gives evidence of agony, with pallor, brow bathed in sweat, and short, spasmodic respiration. The temperature remains normal or is slightly subnormal and the pulse, too, is normal until peritonitis complicates the picture. The pain is localized in the epigastrium, or may occur in the back, the region of the shoulder blade or the right abdomen. There is evidence of free fluid and gas in the abdomen.

A diminution in the symptoms four or more hours later presages a generalized peritonitis and death, unless immediate surgical intervantion is resorted to. Operation within six hours after rupture is favorable to recovery. Operation after thirty-six hours may lead to recovery in a minority of cases. Each hour of operative delay lessens the patient's chances of living.

Subacute and chronic perforations are not so critically dangerous as immediately to threaten life, but in the long run seldom are relieved except by operation. In subacute rupture, leakage is slow, giving rise to a localized peritonitis and adhesions. The syndrome incapacitates the patient and renewal of daily activity usually results in relapse and an eventual state of chronic perforation.

In chronic ulcerous perforation, the roentgenogram, as mentioned previously, reveals an outlying, accessory pocket or diverticulum. The patient will not be incapacitated for work, but experiences chronic pain. Multiple adhesions follow between the gastric wall and neighboring organs, and there may be some local or general peritonitis. Operative procedure is necessary for relief.

When there are symptoms of acute rupture of peptic ulcer, it is necessary to differentiate the diagnosis from that of acute appendicitis, acute hemorrhagic pancreatitis, and gallstone attack. Peptic ulcer perforation gives rise to more violent symptoms and shock than does appendicitis, and exhibits rapid influx of liquid and gas into the abdominal cavity. In pancreatitis, there is a similarity in intensity of shock, but there is less free fluid and total absence of gas in the abdominal cavity. Gallstone attack likewise does not present so severe a symptomatology, does not persist, may be relieved by vomiting, and fluid influx into the abdominal cavity is lacking.

MEDICAL VERSUS SURGICAL INTERVENTION

To the ever-present question whether peptic ulcers shall be treated medically or surgically, perhaps summary answer may be made in this fashion. In their early history, good judgment indicates medical treatment of peptic ulcers. If they persist or recur in spite of modern medical management, better judgment requires recourse

to exploratory and therapeutic surgery. Exploratory surgery is of prime importance when malignancy is suspected because of persistence of symptoms in spite of good ulcer management.

Serious and numerous hemorrhages which threaten life indicate surgery, as does also continued slow bleeding, obstinate to medicinals and resulting in severe anemia. Recalcitrant pyloric obstruction is best treated surgically. And, as mentioned previously, acute rupture of the ulcerated wall demands immediate surgical intervention.

RÉSUMÉ OF MEDICAL TREATMENTS

Medical therapy according to the regimen of Dr. Sippy has for its purpose shielding the ulcer from the corrosive effect of the gastric juice. The Sippy treatment accomplishes this by neutralizing the hydrochloric acid with frequent feedings and the use of alkalies. The patient is required to remain in bed from three to four weeks and may partake of a wide variety of soft and palatable foods. Control of acidity is accomplished by feeding every hour, or in some cases in two, three, or four-hour intervals, with administration of alkalies midway between feedings. According to this procedure, ideal conditions for the healing of the peptic ulcer are maintained when the aspirated stomach contents show absence of free hydrochloric acid during the entire time that food and secretion are present in the stomach. The regimen provides also for control of excessive night secretion of gastric juice.

The Alvarez treatment takes into consideration the economic status of the patient and the frailty of human nature in the face of heavy hospital bills and enforced absence from work. Of the Sippy treatment, Dr. Alvarez says:

> The Sippy diet is not to be despised; it works; but it is too elaborate for the general practitioner and his poorer and more ignorant patients. It calls for considerable enthusiasm and training on the part of the physician, a hospital with excellent interns, and a patient who has plenty of time and money to spend on his cure.

The Alvarez treatment aims to make available a practical course of therapy to the average physician and the average patient. The essential element of the Alvarez treatment consists in a smooth-food diet between meals, seldom any alkaline medication, curtailment of most forms of exercise except walking, and as much rest as may be dovetailed into the patient's daily occupation. A suggested course of frequent feedings is that the patient take with him to his daily work, say a mixture of a quart of milk, two eggs and a half pint of cream. The patient drinks a glassful at 10 A.M., and at 2, 4, 8 and 10 P.M. He may partake of another glassful should he wake during the night. The patient is kept on the Alvarez frequent-feeding diet six months, a year or even longer.

Closely allied with the Alvarez treatment is the Smithies so-called "physiologic rest" treatment. It aims to give the stomach as nearly absolute rest as possible, and starts with a preliminary period of rectal feeding. Dr. Smithies, like Dr. Alvarez, accomplishes his purpose by frequent feedings but limits the diet principally to diluted carbohydrates.

A course of treatment that has found wide favor in Russia is the Jarotzky milkless diet with white of egg and butter. It follows conclusions derived from accurate laboratory experimentation, and aims to give the stomach the greatest possible amount of rest, through a diet of whites of eggs without salt and fresh butter given alternately during the day. The uncooked whites of eggs have the property of fixing the free hydrochloric acid of the gastric juice and also of passing quickly through the stomach into the duodenum. Fresh butter, likewise, suppresses gastric juice secretion and accelerates emptying of the stomach.

SURGICAL TREATMENT

When peptic ulcer, even after thorough

medical treatment, exhibits complications or exaggeration of the severity of the symptoms or recalcitrant recurrences, recourse should be had to surgery. It should be noted that surgical intervention for gastric ulcer is an entirely different problem from surgical intervention for duodenal ulcer.

In gastric ulcer that does not respond quickly to medical measures, surgery is the treatment of choice. It is a well established fact, likewise, that in surgery for gastric ulcer, the ulcer should be removed. Also, early removal of the lesion increases the patient's chances of recovery, should the lesion prove to be malignant, for in gastric ulcer it is not possible to ascertain readily whether or not the lesion is malignant.

In duodenal ulcer, on the other hand, surgical treatment may safely be deferred until after prolonged attempts by medical therapy have failed, and usually it is not necessary to remove duodenal ulcers, as in gastric ulcer cases. However, if duodenal ulcer is giving rise to repeated hemorrhages, removal of the lesion itself is indicated.

CHOICE OF OPERATION

In deciding upon his course of procedure for operating in cases of peptic ulcer, the surgeon may depend upon no set rule of thumb. Rather must he have full knowledge of the various procedures open to him, of their indications and of their possible end-results. His choice of surgical procedure will also be governed according to whether the operation is for primary involvement or recurrence following apparently unsuccessful previous operations.

Let us consider first the surgeon's field of choice in primary ulceration. In gastric ulcer, good results require provision for adequate emptying of the stomach in ordinary digestion and for excision of the lesion. For small gastric ulcers of a diameter of 1 cm. or less, local excision, preferably by cautery, is indicated. It should be combined with pyloroplasty or with gastroenterostomy as the findings warrant. For larger lesions, the surgeon will resort to partial gastrectomy, keeping in mind, however, the high risk associated with the sacrifice of large portions of the stomach.

For duodenal ulcer, gastroenterostomy is the operation of choice. Radical procedure is attended with high risk and is not recommended. A conservative gastroenterostomy has a mortality rate as low as 1 per cent or less, with excellent prospects of satisfactory recovery. Excision of duodenal ulcer with pyloroplasty may be employed as a conservative intervention, but radical operation as though the lesion were malignant is to be condemned. Complete excision is indicated when duodenal ulcer is accompanied by hemorrhage; and, when hemorrhage persists after operation, it is frequently found that another ulcer was present at operation but was undiscovered.

FAILURE OF SURGERY FOLLOWED BY ULCER RECURRENCE

Regardless of the type of primary operation, incidence of recurrence of peptic ulcer symptoms is not more than 6 per cent. Recurrence after pyloroplasty is rare, but pyloroplasty is not always a preferable procedure because it does not give such satisfactory results as does gastroenterostomy. Incidence of recurrence after gastroenterostomy has been reckoned as low as 2 per cent. Gastrectomy exhibits a distinctly higher probability of recurrence.

Recurrence of peptic ulcers after operation present the therapeutist with a problem requiring exceedingly fine distinctions. Careful analysis must differentiate the probable cause or causes of the recurrence, and further procedure must be based thereon. The factors influencing recurrence are various. Among them may be enumerated reulceration of the old lesion, development of a new lesion, or additional ulceration which was present at operation but not discovered. There is the possibility, also, of persistence of a causative dyspepsia or superimposition of causative dyspepsias that had not previously existed.

MODE OF TREATMENT FOR RECURRENCE AFTER OPERATION

Response to medical treatment of a recurrent peptic ulcer after operation does not result so satisfactorily as does medical treatment for primary ulcer. Consequently more recurrent ulcer patients come to operation than do primary ulcer patients. In this connection it might be interpolated that the practitioner need not hesitate to institute prolonged medical therapy in an endeavor to avoid repetition of operation, for a recurrent ulcer seldom terminates in malignancy.

Surgical procedure for recurrent ulceration after previous operations may be roughly divided into two classes, according to whether the symptoms are caused by a new lesion or by reulceration of the old lesion.

New ulceration after pyloroplasty should be excised and a secondary plastic operation or a gastroenterostomy performed. New marginal lesions involving the stomach or jejunum after a previous gastroenterostomy may be excised; and, if the primary duodenal ulcer has entirely healed without deforming the structures, the original natural pathway between stomach, pylorus and duodenum may often be satisfactorily restored. The stomach and the jejunum will in such instances be disconnected and the gastroenterostomy discontinued. Even if the original duodenal ulcer has not entirely healed, the same procedure may often be maintained, excising the duodenal lesion and reconstructing the pylorus and the duodenum. Partial gastrectomy and partial duodenectomy may be necessary in addition.

When the recurrence appears to be a reactivation of an old duodenal ulceration, especially after previous gastroenterostomy, it will usually be found that the artificial gastroenterostomy opening has not been well located, is too small and fails to function properly, though the gastroenterostomy itself does not exhibit ulceration. The best procedure is to excise such duodenal lesions, preferably by cautery, and explore for any additional previously undiscoverable lesions on the posterior wall. Again it is frequently favorable to disconnect the stomach and the jejunum and to reconstruct the pyloric outlet and the duodenum.

In cases where old duodenal ulcers have broken out anew in spite of well chosen and properly functioning gastroenterostomy, it may be necessary to resort to a Billroth II operation and partial duodenectomy.

The most difficult problem for the therapeutist is recurrence of gastric ulceration after previous partial gastrectomy, for further resection is extremely unfavorable and hazardous. In recurrence following the Billroth I type of resection, gastroenterostomy may prove satisfactory. After a Billroth II type of resection, a preliminary jejunostomy may be performed, permitting a more radical secondary procedure.

CONCLUSIONS

Summarizing my brief exposition on peptic ulcers, I will call to mind that, after repeated trials by medical management have failed, perhaps in 10 to 12 per cent of cases, refractory peptic ulcer should be given the benefit of surgical intervention. In determining the line of treatment, it is of greatest importance that internist and surgeon collaborate to the best interests of the patient. Great patience will need to be exercised by both the patient and the therapeutist, for it will frequently be necessary to prolong the treatment over a period of months or even a period of years. The ease of recurrence will discourage both the patient and the practitioner. Accessory to either medical or surgical intervention will be the necessity of so re-ordering the patient's daily activity and diet as to eradicate inimical factors and to set up ideal conditions for repair and prophylaxis. Each patient will be a clinical picture unto himself, requiring searching out of particular causative factors and individual modes of treatment and limitations of habits of living.

PARTIAL GASTRECTOMY

IN THE HANDS OF THE GENERAL SURGEON*

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IN visiting the various German clinics one finds that the prevalent opinion throughout Germany today is that both gastric and duodenal ulcer, in the face of the failure of conscientious medical treatment, is to be treated with partial gastrectomy in one of its forms. Gastroenterostomy is called upon in those cases where the patient's condition demands the simplest of procedures; where the operative difficulties would involve unwarranted risk; and in some cases of pyloric stenosis. Local resection, inversion of the ulcer, pyloroplasty and pylorectomy are seldom used.

The well-trained surgeon should be capable of doing any and all of the procedures with equal skill. His failures will not often be explained by a failure of the operative method, per se, but as an error in not choosing the appropriate method for the case. He must be capable, after a careful survey of the given pathology, of choosing correctly that method which promises for the individual case the maximum opportunity for cure with the minimum risk. To change from one operative method to another with the procedure well under way is to invite disaster.

The rules which have been adopted for the selection of method in this clinic are:

The method of Billroth 1 shall be used in all cases of ulcer lying in the region of the duodenum, pylorus and antrum in which the pathology presents no unusual difficulties to the carrying out of the procedure.

The Billroth 2 (Mikulicz-Kronlein-Reichel modification) shall be substituted for the Billroth 1 operation in ulcer lying high above the pylorus; in those cases where the freeing of the duodenum from the pancreas is beset with such difficulties as to make it unwise to use the cut end of the duodenum in the reanastomosis with the stomach; where the lumen of the duodenum is so contracted as to warrant the fear of a later partial stenosis at the site of anastomosis; and lastly, where the reunion of the stomach and duodenum would necessarily involve tension at the suture-line.

In routine practice one-third of the stomach (antrum) with the pylorus and the adjoining portion of the duodenum has been removed. Removal of the ulcer, where possible, has been considered an essential part of the operation. Routine appendectomy has been not the rule but rather the exception.

Gastroenterostomy is done as stated here: in those cases where the patient's condition demands the simplest of procedures; where the performance of resection would involve unwarranted operative risk; and in some cases of pyloric stenosis. Gastroenterostomy with occlusion of the pylorus, because of the unhappy results experienced, has not been done during the past five years.

The series presented contains 211 patients operated upon by 11 different operators, all of whom had had a minimum intensive training of five years in this clinic before being allowed to do partial gastrectomy.

Of the 211 patients, 113 were operated upon by the method of Billroth 1; 58 by the modified Billroth 2 method; and in 40, gastroenterestomy was done, in 9 of whom pyloric occlusion after the method of von Eiselsberg was performed.[7]

The shortest postoperative period through which the cases have been followed is eighteen months and the longest ten years. Personal interview and re-examina-

* From the Chirurgische Klinik und Poliklinik der Universität Halle-Wittenberg, Prof. Fritz Voelcker, Director.
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tion were done where possible, the other cases being investigated by an exhaustive questionnaire in which space was provided for the patient to discuss his progress from the date of dismissal from the hospital up to the present day. The answers were for the most part entirely satisfactory, the replies being clear and concise. Three hundred cases were investigated, of which 89 were eliminated because of insufficient data, etc.

METHOD OF CLASSIFICATION OF RESULTS

One is constantly disappointed, in reading the literature on this subject, by one's inability to draw definite conclusions from many of the articles because of the multiplicity and inaccuracy of the terms used in qualifying the postoperative results. Such terms as "good results," "permanent results," "satisfactory results," etc., without further classification, convey nothing definite to the reader. If we are, in the future, to arrive at a more definite or a more unanimous opinion as to the worth of the various operative procedures about which there is such a divergence of opinion, then a stricter and preferably a standardized classification will be necessary. Perhaps with a more definite classification in use there will be fewer reports of 98 per cent of "satisfactory results."

The classification which I offer here has been taken in each of the four groups from the patient's own description of his present condition.

Cured: Those patients who have been followed for a period varying from eighteen months to ten years after operation and who have remained absolutely symptom-free on a general diet and who have been able to resume their former occupations.

Greatly Improved: Those who are on the whole symptomless but who after exhaustion or dietary indiscretion (usually alcohol) have occasional eructations and a feeling of fulness in the epigastrium.

Improved: Those who must avoid some of the heavier foods and who after overwork or dietary indiscretions suffer sour eructations and dull pain in the epigastrium.

Unimproved: Those having similar symptoms to those suffered previous to operation or in whom the symptoms are alleviated but still appear periodically. Lastly, all patients who still vomit, whether frequently or only occasionally.

DIET

It is fitting in judging this classification to remember that this series dates from 1919 to 1927 and that during the period from 1916 to 1925 the people as a whole were greatly undernourished and had learned to eat any and all types of food. Thus, most of the patients treated in this clinic are absolutely intractable toward the maintenance of a postoperative diet. As soon as they are dismissed from the clinic they admit returning to their former diet of sausage, brown bread, the rougher vegetables and usually beer. When, then, dietary indiscretion is voluntarily admitted, one may take it in the extreme meaning of the phrase.

OPERATIVE RESULTS

BILLROTH I

A total of 113 cases, 73 of which were of the stomach, 23 of the duodenum and 17 of the pylorus.

	Stomach (73)		Duodenum (23)		Pylorus (17)	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Group 1 cured.....	43	58	12	53	3	17
Group 2 greatly improved.....	8	11	3	13	1	5
Group 3 improved.	10	7	4	17	7	41
Group 4 unimproved.....	12	23	4	17	6	37

After a careful consideration of the preoperative and postoperative condition of those patients falling into Group 2 it is to be concluded that they have been so much benefited, that operation, not forgetting the risk, has been justified. If then we are allowed to combine Groups 1 and 2 we see that 69 per cent of the stomach ulcers and 65 per cent of the duodenal

ulcers have been greatly benefited by operation.

"Ulcers on the pylorus" have been perforce so classified since the operator had in these cases classified an ulcer lying anywhere on the pyloric ring as "pyloric ulcer." We are aware that if one classifies these ulcers according to their relation to the pyloric vein one may seldom speak of a true pyloric ulcer. I am unable to explain the poor results obtained in the 17 cases in this group.

BILLROTH 2

A total of 58 cases, of which 30 were of the stomach, 25 of the duodenum and 3 of the pylorus.

	Stomach (30)		Duodenum (25)		Pylorus (3)	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Group 1 cured	18	60	13	52	2	66⅔
Group 2 greatly improved	7	23	3	12		
Group 3 improved	2	7	6	24		
Group 4 unimproved	3	10	3	12	1	33⅓

In combining Groups 1 and 2 as under the Billroth 1 classification, we see that 83 per cent of the stomach cases and 64 per cent of those of the duodenum have been greatly benefited by operation. The 3 cases of pyloric ulcer are self-explanatory.

GASTROENTEROSTOMY

Since gastroenterostomy was performed in those cases in which resection seemed contraindicated, the figures will also be given. The gastroenterostomy series is really too small to allow of its classification in percentage. The figures are merely so given to permit of rapid comparison with the two tables given here.

	Stomach (9)		Duodenum (9)		Pylorus (13)	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Group 1 cured	2	22	5	55	5	38
Group 2 greatly improved	3	33	2	22	3	23
Group 3 improved	..	..	1	11	1	7
Group 4 unimproved	4	45	1	11	4	32

Of the nine cases of gastroenterostomy with occlusion of the pylorus after the method of von Eiselsberg,[7] only 3 could be classed as cured, the others being classified as unimproved.

MORTALITY

It is here under this heading that one who seeks guidance from the literature may dwell with the greatest profit, for the operative results in the surviving patients, even though they be 100 per cent, must be weighed against the fatalities encountered in the use of the method.

	Billroth 1	Billroth 2	Gastro-enterostomy
No. of cases operated upon	164	126	105
Deaths	15	17	5
Mortality rate	9.1%	13.8%	4.7%

MORTALITY STATISTICS

Cause of Death	Gastro-enter-estomy	Billroth 1	Billroth 2
Pneumonia	...	5	3
Emboli	...	..	2
Shock	...	..	1
Hemorrhage	...	1	2
Ileus	1	1	
Dilatation of the stomach	...	1	
Perforated duodenal ulcer			
5 days postoperative	1		
14 days postoperative	1		
Leakage of inverted duodenal stump (peritonitis)	...	..	2
Leakage at site of anastomosis (peritonitis)	...	1	1
Fresh ulcerations (hemorrhage)	...	..	1
Peritonitis	1	4	3
Unexplained	1	2	2
Total Number of Deaths	5	15	17

(The figures here given are taken from the entire series and not alone from those cases which have been followed.)

That the Billroth 2 operation should carry a mortality rate 50 per cent higher than that of the Billroth 1 is not the experience of most. It must be considered

that according to the rules given here the Billroth 2 procedure would be used in the most difficult cases. It is striking that of the 17 deaths from this operation, 14 of these patients were operated upon for ulcers of the duodenum. It is true that the performance of the operation takes somewhat more time than that required for the Billroth 1 but this could hardly be considered a factor in our higher mortality rate since there was but 1 death which was attributable to shock. On the other hand there were 2 deaths from peritonitis arising from an ineffective inversion and consequent leakage at the suture-line of the duodenal stump. These 2 cases as well as the third case of peritonitis, which could be traced to a leakage of the suture-line between jejunum and stomach, must be charged to technical errors, since this accident should be avoidable in the Billroth 2 procedure.

The freeing of the duodenum from the pancreas in those duodenal ulcers which are firmly adherent to, or, penetrated into the pancreas, is perhaps the most hazardous step in the performance of this operation. In freeing the duodenum it is too often the case that the serosa and muscularis of its posterior wall are stripped away and the operator is confronted with the task of inverting the stump in the face of a deficiency of the serosa of the posterior wall. Under these conditions the inversion is usually inefficient and the operative risk is greatly increased.

The second danger in the freeing of the duodenum is the wounding of the head of the pancreas with the possibility that the sutures will later be digested by the pancreatic secretions.

The experienced surgeon will most often know from his initial survey of the pathology whether or not he will be able to free the duodenum from the pancreas without inviting disaster. When he is convinced that the risk incurred in so doing would be unwarranted he will be wise in completing the procedure with a more conservative operation. One is not justified, once having started to perform a Billroth 1 and having freed the duodenum at the cost of stripping the posterior wall of serosa and muscularis, in then deciding that one must complete the procedure with the modified Billroth 2 operation.

The 1 death from peritonitis in our Billroth 1 series resulting from a leakage at the suture-line between the reunited stomach and duodenum must be somewhat more kindly regarded, since this error has been made by the best technicians and has been consequently a long-warned-of hazard.

Many have taken their stand against the operation of Billroth 1 because of the fear of postoperative dilatation of the stomach. One of the 15 deaths in our series could be ascribed to this cause and it was a worrisome postoperative complication in many of the cases.

The deaths following gastroenterostomy were less noteworthy, with the exception of the two patients who died five and fourteen days postoperatively, death being due in each case to a perforation of the duodenal ulcer.

In comparing the mortality of this series with that of several representative clinics it is to be seen that it is not excessively high. Louria[8] reporting the cases from von Haberer's clinic in Graz during the years 1925 to 1927 reports a general mortality of 8.4 per cent; Berg[9] reports an 8 per cent mortality from the Mt. Sinai Clinic; and Magazinik[10] reported in 1929 as a result of a questionnaire sent to the various Russian surgeons a general mortality of 12.2 per cent in partial gastrectomy.

The point raised in the study of these statistics is that the average general surgeon must expect a mortality of 8 to 10 per cent in the use of these methods. It is to be hoped, however, that this mortality can be decreased through a greater experience in choosing the operative method most applicable to the case and in learning once and for all that ulcers which have penetrated into or are strongly adherent to the pancreas are to be regarded

with the utmost respect and should probably most often be handled with one of the more conservative operative procedures.

That the mortality rate can be cut to a minimum is shown by the results of Bastianelli[11] whose mortality is but 2 per cent; Moynihan[12,13] reports a mortality ranging from 1.6 per cent to 3 per cent during the past ten years; Finsterer in 850 resections had a mortality of 3.8 per cent and von Eiselsberg in 449 cases a mortality of 3 per cent.[14,15]

In the last analysis the task of relieving the patient who continues to suffer from the symptoms of chronic ulcer despite rigid medical treatment is that of the surgeon. It should be the aim of the general surgeon to offer this relief while attempting to reduce the risk associated with these operative measures.

COMMENT

In combining the figures of the Billroth 1 and 2 procedures it can be said that 59 per cent of the stomach ulcers have been cured and 17 per cent greatly improved; 7.5 per cent have been improved and 16.5 per cent must be classed as unimproved.

Of the duodenal ulcers, 52 per cent have been cured, 12.5 per cent greatly improved, 21 per cent improved and 14.5 per cent remain unimproved. The end-results of the comparative figures of the Billroth 1 and 2 procedures may, in such a small series, be looked upon as quite the same but the half again higher mortality of the Billroth 2 operation overrides all other claims in this series.

It is to be seen that the results in this series are not to be compared with those published by surgeons having a very much larger material and doing the entire operating themselves. Finsterer[14] in a series of 850 cases reports 97 to 98 per cent as cured; de Takats,[16] 226 cases with 84 per cent cured and von Haberer in his carefully followed series of 2310 stomach resections reports but 0.6 per cent of recurrent ulcers.[17]

It is, of course, to be taken for granted that by and large the surgeon with the greatest experience will obtain the best results. The point in question is: What results may the well-trained surgeon working with a comparatively small material hope to obtain? I think that our statistics answer this in part.

Is the general surgeon justified in continuing to perform partial gastrectomy with its average mortality of 8 to 10 per cent balanced against 70 to 75 per cent positive results? I think that we have profited greatly from our previous mistakes and that the ideal set for us by those whose results have been so brilliant is within reach.

We must seek a decrease of the mortality rate in the conquest of our previous technical errors. The root of these has perhaps not been a lack of technical training but rather a failure in judgment. One must be able after a survey of the given pathology to choose with decision and accuracy the most applicable method to be used in its eradication.

In approaching the ulcers of the duodenum which are strongly adherent to or which have penetrated into the pancreas we must shackle our courage and handle them by the conservative method advised by Wilkie[18] and Moynihan. If resection is thought necessary it is then perhaps wiser to leave the ulcer untouched. Finsterer[19] has reported 53 cases followed for from two to twelve years, with 88 per cent healing, the operation of Billroth 2 having been performed and the ulcer left undisturbed. Flörcken[20] reports 104 cases followed for from five to seven years with 90 per cent healing in which radical removal of the ulcer was impossible but in which cases the modified Billroth 2 procedure was carried out. In truth, to know one's limitations is to defeat failure.

One must question if our results would have been better had routine appendectomy been done. This would be answered in the affirmative in most of the American and English clinics but with very much less enthusiasm in most of the German and Austrian.

It is the opinion of most that the maximum results are only obtained when a strict diet is followed for from six to nine months after operation. It is probable that had this been possible our total number of cured cases would have been greater.

In conclusion it may be stated that no matter what type of resection one may choose to do, that type must fit the given case better than any other one. I believe that the rule for the selection of method given here and used in this clinic is as good as any which we at present know, if we add thereto, that ulcers of the duodenum which are strongly adherent to or penetrating into the pancreas are to be treated by conservative surgery.

A point to be stressed is that the Billroth 2 (Mikulicz-Kronlein-Reichel) operation is not to be considered the step-brother and to be selected at the last minute because of the unlikelihood of completing the procedure with the contemplated Billroth 1. It is at this stage that failure of judgment is escorted by technical error.

SUMMARY

1. One hundred seventy-one cases of patients having ulcer of the stomach or duodenum operated upon by the method of Billroth 1 or the modification of Billroth 2 (Mikulicz-Kronlein-Reichel) are presented.

2. Of 113 patients operated upon by the method of Billroth 1, 73 cases were of the stomach (antrum), 23 of the duodenum, and 17 of the pylorus. In those ulcers of the stomach 58 per cent were classified as cured, 11 per cent as greatly improved and 12 per cent as unimproved; the remaining 19 per cent lying between the two latter groups. In the duodenal ulcers, 52 per cent could be classed as cured, 13 per cent as greatly improved, 17 per cent as improved and 17 per cent as unimproved.

3. The mortality rate in the Billroth 1 operation was 9.1 per cent.

4. Of 58 patients operated upon by the modified Billroth 2 procedure, 30 cases were of the stomach, 25 of the duodenum, and 3 of the pylorus. In those ulcers of the stomach, 60 per cent were classed as cured, 23 per cent as greatly improved, 7 per cent as improved, and 10 per cent as unimproved. In the duodenal ulcers, 52 per cent were classified as cured, 12 per cent as greatly improved, 24 per cent as improved and 12 per cent as unimproved.

5. The mortality rate in the modified Billroth 2 operation was 13.8 per cent. Of the 17 deaths 14 were operated on for ulcer of the duodenum.

6. The results obtained in ulcer of the stomach with the modified Billroth 2 operation were somewhat better than those obtained with the Billroth 1, but in this small series one could in general say that there is little to choose in the end-results of the two methods.

7. The figures from a small series of gastroenterostomies are given. It is worthy of note that of the 5 deaths in 105 cases 2 were attributable to perforation of the duodenal ulcer on the fifth and fourteenth postoperative day.

8. Gastroenterostomy with the occlusion of the pylorus after the method of von Eiselsberg has given unhappy results.

9. The rules followed in this clinic for the selection of the operative method are given.

10. Ulcers of the duodenum which are strongly adherent to or have penetrated into the pancreas are to be operated upon conservatively.

11. Billroth 1 and Billroth 2 are to be considered as two entirely different operations, each having its definite indications. They are not to be used interchangeably or the one substituted for the other with the operative procedure well under way.

12. The results obtained by the general surgeon will only show improvement after he has thoroughly learned to fit the operative procedure to the pathology and to respect ulcers of the duodenum which have become adherent to the pancreas as carrying the highest operative risk.

[*For References See p.* 313.]

MESENTERIC THROMBOSIS

REPORT OF AN UNUSUAL CASE, FROM AN ETIOLOGICAL STANDPOINT*

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THE reason for reporting this case is its peculiar cause.

Private First Class H. W. P. 64th Coast Artillery, was admitted to Tripler General Hospital, 11:45 P. M. Saturday, December 7, 1929, complaining of considerable abdominal pain. Suspected appendicitis was ruled out. An enema was given, which caused vomiting followed by relief. A previous admission in November 1929, with similar symptoms, is recorded, and relief after treatment.

Tuesday, December 11, patient went to Dental Clinic and had a tooth extracted. Following this, patient was seized by a violent cramping, abdominal pain, right side. He got out of chair and doubled up on floor, complaining bitterly of his pain. The urologist was called and immediately catheterized the ureters and did a pyelogram, which showed both kidneys and ureters as normal. Patient complained of a sticking sensation in his abdomen while on floor at Dental Clinic.

I was asked to see patient about noon by the Chief of Medical Service, Major William C. Whitmore, Medical Corps, and we made a diagnosis of suspected mesenteric thrombosis and advised immediate exploration. A mid-right rectus incision revealed an excessive peritoneal fluid, blood tinged. The ileum was dark blue and its mesentery intensively red and congested; there was no notable distention of bowel, the thrombotic mesentery and intestine supplied extended from the ileocecal valve for about 6 or 7 ft. up toward jejunum. The cecum showed marked congestion of lymph vessels.

The bowel was brought out of the peritoneal cavity and carefully examined by stripping it through the fingers, when at its upper level my glove caught on a foreign body, and examination showed two small pieces of fine wire 1 in. and 1½ in. long, respectively. These were removed from the mesentery about 1½ cm. from the attachment to bowel. One piece apparently passed through a branch of the vasa intestinal tenuis and caused the thrombosis.

The wire was very fine, about the size used in window screening. The patient has no recollection of holding wire in his mouth. It is not a dental broach or the needle wire from a hypodermic.

The conclusion is that the wire was swallowed with his food. This caused some gastrointestinal disturbance during his November admission and again in December. The sticking sensation December 11 was caused when the wire left the intestine and pierced the mesentery and the intense abdominal angina, when the actual thrombosis occurred.

After stripping bowel through fingers, its color improved and it was then returned to peritoneal cavity.

The patient made an uneventful recovery.

Note: "A case reported by J. M. Black, F.R.C.S., *Brit. M. J.*, December 28, 1929 in which a piece of wire two (2) inches long perforated the ileum. Symptoms: pain. A diagnosis of appendicitis made—explored and wire removed. Omentum had closed over wire at site of perforation."

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THE TREATMENT OF INTESTINAL PARASITISM

BY INTRADUODENAL INSTILLATIONS*

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WITHIN a very short period following the introduction of the duodenal tube into clinical practice, attention was directed to its use as a means for administering medication and for the therapeutic irrigation of the small bowel. The earliest step in the process of intubating the duodenum must be credited to Hemmeter, though Einhorn in 1910 was the first to succeed in perfecting the instrument and the technique for practical clinical purposes. The earlier pioneers in the field were primarily interested in the diagnostic side, chiefly in securing the contents of the upper intestinal tract for more careful study and analysis.

In 1911, Gross called *particular* attention to the therapeutic possibilities of the new method, having interested himself in the question of lavage of the duodenum in cases of chronic duodenal catarrh, cholelithiasis, and persistent icterus. For this purpose he employed solutions of Carlsbad salts and of bismuth subnitrate, and claimed to have observed beneficial results.

Harvey Beck, approximately a year later, recorded the administration of powdered ipecac root held in watery suspension or in emulsion, by way of the upper intestinal tract through the agency of the duodenal tube. Seven intractable cases of chronic entamebic dysentery were reported to have been successfully treated in this manner.

M. Ernest Jutte, later in 1912, pioneered the idea of transintestinal lavage by means of massive amounts of fluid introduced through a slightly modified duodenal tube. The solution employed for the purpose consisted of a definite hypertonic saline mixture, which escaped absorption along the intestinal tract, and was thus more productive of complete flushing of the intestinal contents than was effected by former methods. Further contributions from the same author supplemented his earlier views on the subject and led to suggestions for a wider application of the plan. In the last article on the subject published by Jutte in 1917, he made note of the possible value of transintestinal irrigations for ridding the intestinal tract of worms and other animal parasites. This same idea, had, however, been brought forward previously by Paleski in 1915. In discussing the therapeutic indications of transduodenal lavage, he stated that the measure should prove an extremely valuable one in the treatment of intestinal worms or intestinal parasitic diseases, using the irrigating salt solution as a vehicle for medicinal substances to bring them into close contact with the unfriendly host in the intestinal canal, at the same time causing their expulsion by the thorough intestinal irrigation.

As a further stepping stone toward the development of the idea of the relationship of duodenal intubation to the treatment of intestinal parasitism, Hemmeter in the course of an exhaustive résumé of the subject of Giardia intestinalis presented before this Society in 1920, entered into a detailed description of the treatment of this intractable upper intestinal infestation by means of intraduodenal medication. At this time Hemmeter drew attention to the great difficulties experienced in overcoming Giardia infestation which he ascribed to the migration of the organisms into the crypts of the intestinal glands as well as into the bile ducts and gall bladder. Agents designed for the destruction of this type of protozoal infection, therefore, must act not only

*Read at the Thirty-third Annual Meeting of the American Gastro-Enterological Association, Atlantic City, May 5 and 6, 1930.

locally but likewise by absorption into the general circulation. Hemmeter believed that hexamethylenamine might meet this indication as an antiparasitic drug since formaldehyde could be detected by him in the bile shortly following its absorption into the portal system. In other more refractory cases, methylene blue (50 c.c. of 0.5 per cent solution) was suggested, likewise, by administration through the duodenal tube because of the penetrating effect of the dye in the tissues, as well as its destructive action upon giardia in vivo.

In 1921 the writer himself published an apparently successful clinical result in a case of intestinal giardiasis by massive transduodenal irrigations with Jutte solution upon ten successive days. There was, however, a subsequent reappearance of the infection in this case, and since failure was also recorded in the use of hexelethymine and methylene blue in a series of further observations, the intraduodenal instillation of 6 to 9 dg. of arsphenamine dissolved in 90 c.c. of water was attempted. More successful results seemed to follow this procedure, which was made the basis of a further report by me in 1922. I might add further at this time that subsequent experiences in other cases of Giardial infection have rather confirmed the early optimism recorded with this method. The destructive action of arsphenamine upon Giardia was first described by Yamanorf in 1917 in experiments upon mice, and was afterwards confirmed by Carr and Chandler in a series of human cases. The latter authors gave 6 gm. doses of the drug for four successive intravenous injections each five days apart. Kantor in 1923 stressed the important fact that salvarsan and other arsenicals are excreted mainly through the intestinal glands and biliary tract and recommended arsphenamine per rectum as well as intravenously for giardial infections. Subsequent writers, including both Chandler and Kantor, have pointed to the importance of employing a sufficiently large dosage of the arsenical preparations, since otherwise tolerance to the drug is readily established by the organisms. Hollander found intravenous injections of arsphenamine (dose not given) unsuccessful in 2 cases reported by him, but achieved a cure in a third case by alternating the intravenous injections with duodenal lavage of 25 per cent solutions of magnesium sulphate. Lyons also commended the combination of the usual duodenal douches of magnesium sulphate with intravenous injections of arsphenamine in giardiasis, because of the association noted by him between this type of protozoal infection and gall tract disease. He advised caution, however, in judging cures of giardia infection prematurely because of the well known tendency to relapse.

A further interesting contribution to the general subject of the therapeutics of intestinal parasitism by intraduodenal irrigations was made by Rivas in 1926. Both protozoal and metazoal parasites in the human intestinal tract, according to Rivas, are subject to destruction when exposed, for a comparatively brief period, to temperatures ranging from 45 to 47°C. The detrimental effect of even slight alterations in temperature may be observed not only upon the life cycle of certain types of bacteria, as tubercle and anthrax bacilli, but upon protozoal organisms, worms and other forms of animal life as well. The plan suggested by Rivas for the more or less complete destruction and removal of parasitic infestation of the intestinal tract involves the introduction through the duodenal tube of a liter or two of normal saline solution with a temperature reading as high as 47°C. The importance assigned to the relatively high temperature of the solution is stressed above that of the effect of the flushing out of the organisms with the large amount of fluid employed. It is necessary that the parasites within the lumen of the bowel be exposed to the increase in temperature for a period of not less than ten minutes. For this reason, those organisms having their habitat within the large bowel are to be reached principally by colonic flushings

preferably in combination with instillations from above. As a further part of the technique employed by Rivas, 2 or 3 oz. of a 30 per cent solution of magnesium sulphate are introduced into the duodenum prior to the use of the heated saline solution, and this is to be repeated once or twice during the process of the flushing in order to insure more prompt evacuation from the bowel. The 234 cases of intestinal parasitism reported to have been successfully treated by the author with this thermal method were classified by him as follows: Entameba histolytica, 103; Oxyuris vermicularis, 21; Trichocephalus, 6; Giardia, 13; Trichomonas, 9; tapeworm, 23; hookworm, 56; and Trichina, 3.

Hall and Shillinger in an experimental study upon dogs with the Rivas' plan found that temperatures of 52° to 47°C. resulted in a very high percentage of removal of the infecting worms, but one-half of the dogs died within two days, showing evidence of necrosis of the intestinal mucosa. These writers suggest, therefore, that the temperature of the solution within the duodenum, should not exceed 45°C. and that the total amount of solution employed not reach above 8 l. With these precautions, they believe that the plan should prove entirely safe with the human host as well as in lower animals, and should show marked efficacy in removing worms, especially where anthelmintic drugs have been found to be of little value.

From this brief résumé of historical data, it will be seen that the trend of thought in reference to the elimination of animal parasites from the human intestinal tract has undergone some very definite and progressive changes. The fundamental principles underlying the selection of successful measures for the removal of the offending parasites, according to present day standards, should include first, safety to the host; second, the maximal destruction effect of the selected plan upon the parasite either by direct local action or by absorption into the blood stream as is necessary in some instances; third, the rapid expulsion from the intestinal tract of the dead or stunned parasites before reinfection might take place.

As a group, the parasites infesting the intestinal tract have always proved more or less defiant to the various agencies directed toward their destruction and removal. While a few are acknowledged to be subject to complete eradication by certain specific drugs, many still remain refractory to all known methods of procedure. The Entamobae histolyticae, though deeply imbedded in the tissues, are nevertheless destroyed by the specific action of ipecac and its derivatives, but this drug has practically no effect upon other intestinal parasites. Hookworm infection may be removed effectively by the use of oil of chenopodium and certain carbon derivatives, chiefly carbon tetrachloride, chloroform, and tetrachlorethylene. These drugs are also found to be useful in other of the nematode infections, but not to the same degree as is the case with the hookworm. Santonin possesses definite value in its effect upon Ascaris, and to a lesser degree upon Oxyuris vermicularis. Under certain ideal conditions of administration, the various teniae are susceptible to the stupefying action of such drugs as pelletierine and male fern, but expulsion from the intestinal canal must be fairly rapid.

This constitutes the sum total of the proved efficiency of drug therapy upon intestinal parasites, both protozoal and metazoal, as established by modern day knowledge. Chandler and Chopra state the case succintly in reference to the intestinal worms by observing that, "Hookworms and their allies, Ascarids and flukes alone are fairly susceptible to therapeutic agents, tapeworms are only moderately susceptible, and Oxyurids, Strongyloides, Trichuris and others still hold out a large extent against all efforts to dislodge them." Furthermore, among the protozoal group, excluding the amebicidal action of ipecac, specific measures of control are still lacking

in the case of Balantidium coli, as well as with the many species of flagellates with the possible exception of Giardia intestinalis.

Doubt is still expressed by some authorities in regard to the necessity of removing certain of the intestinal parasites. The baneful influence exerted by the parasites upon their host assumes many forms and varies, of course, with the type of the invading organism, as well as with the susceptibility of the individual. Some are universally acknowledged to be frankly pathogenic, as for example, Entamobae histolyticae, Balantidium coli, and hookworm. A considerable question still exists, however, in many sources in reference to the pathogenic possibilities of other of the parasites. The supposedly non-pathogenic group includes even such a highly motile and migrating flagellate as the Giardia, also the Strongyloides, which buries itself resistantly below the bowel mucosa, the Ascaris, Oxyuris, and Trichuris all of which are tissue burrowers and to a certain degree bloodsuckers. The belief in the harmlessness of many of the parasites is in great degree based upon their general prevalence without apparent clinical symptoms. This condition exists, however, in the case of parasites unquestionably accepted as pathogenic. Caldwell and Caldwell state that the difference is one of degree and not of kind, as witness, the large proportion of people infected with hookworm who do not exhibit measurable symptoms. The same is true of Entamobae histolyticae infections, since it is known that approximately 9 per cent of the world's population are infested with this organism without presenting definite clinical manifestations. Furthermore, the fact must be recognized that parasital infection exists in connection with other and in many instances more serious organic disease but none the less this does not prove the harmlessness or the innocence of the invaders. After study and observation of intestinal parasitism in its many phases over a course of years, I am myself convinced that all intestinal parasites are either definitely or potentially pathogenic, some of course to a greater degree than others. Moreover, the presence of these foreign invaders should in each instance call for steps for their prompt removal.

The duodenal tube, I believe, has come to occupy a definite place among the means at our disposal for assisting in the crusade against these lowly offenders. Since rapid expulsion of the organisms constitutes one of the fundamental principles in antiparasitic therapy, transduodenal irrigation unquestionably offers a most valuable means to that end. The author has, during the past two years, experimented extensively with the Rivas, thermal plan. Instead of the normal saline intraintestinal flush as advocated by Rivas in conjunction with magnesium sulphate installations, I have substituted hypertonic irrigations heated to temperatures not exceeding 45°c. No untoward effects have been noted in any of the cases. The amount for each administration has averaged 1000 c.c. and in no instance has been allowed to exceed 2 l. Protozoal organisms because of their tendency to penetrate or migrate into the deeper recesses of the bowel wall, are probably never completely eradicated by this method, certainly not in my experience. There is no doubt, however, that those parasites lying free within the intestinal lumen can be, to a great extent at least, washed out by the Rivas' method. In the case of worm and fluke infections, as confirmed by Hall and Schillinger's experiments in dogs, a large percentage of the infecting organisms can be killed and removed by vigorous thermal irrigations. Nevertheless, when one considers the grappling action by means of which the heads of the various nematodes and cestodes affix themselves to the intestinal mucosa, it is not reasonable to suppose that surface washings may always suffice. In our experience with Trichuris and Strongyloides, for example, many of the worms were washed out; but a renewal of the infections appeared subsequently. However, two of the Strongyloide cases

have shown no trace of larvae in the feces after a period of ten and eight months respectively. In several cases of oxyuris infestation no evidence of the worms has been found after a prolonged and apparently sufficient lapse of time. A combination when possible of the destructive and stupefying effect of drug therapy in conjunction with transduodenal flushing is to be looked upon as the more ideal plan. The drugs themselves, it should be remembered, may be administered to the patient directly through the duodenal tube instead of by mouth. As stated previously, the author has found the intraduodenal administration of Arsphenamine more effective upon giardial infections than when employed by the intravenous route, as advocated by others. Furthermore, Kantor has succeeded with the introduction of oil of chenopodium in a dosage of 2 c.c. through the duodenal tube in cases of hookworm infection. Under proper precautions, there seems to be no reason why carbon tetrachloride might not be administered in a similar manner either alone or in combination with the oil of chenopodium. The way has thus been opened for what would appear to be a more effective means of administering other drugs by the duodenal route. Certainly, the expulsion of the parasites following the inhibiting effect of the specific drug can be greatly promoted by the combined employment of large amounts of irrigating fluids through the agency of the duodenal tube.

DISCUSSION

Dr. Smithies: One must not forget that these protozoa infest the biliary tract, and they are *not* so harmless as some physicians would like to have us believe they are.

We have reported 36 cases of infestation of the biliary tract containing protozoa and in 14 of these we secured operative proof.

Dr. Morrison: I was very much interested in Dr. Simon's paper, because it stresses the usefulness of the duodenal tube. In 1922, Drs. Wiest and Gantt, who were then in our clinic at the University of Maryland reported a number of cases of tapeworm treated effectively by the administration of Oleoresin of male fern mixed with mucilage of acacia through the duodenal tube. We have also successfully treated cases of lamblia infection and amebic dysentery by instilling directly into the duodenum through the tube neoarsphenamine according to Dr. Simon's method and powdered ipecac respectively as advocated by Beck.

Dr. Simon (*closing*): I did not have opportunity in reading the paper to stress one important point, namely, that one or two installations of arsphenamine do not suffice in the treatment of the giardial cases. We have been in the habit of distributing the treatments a week apart and continuing them over a period of from six to eight treatments.

In reference to the use of arsphenamine intraduodenally, an advantage is noted in that there is no upset or other constitutional effect, such as is met with by the intravenous route at times. In cases of Strongyloid infection, the behavior of the worm is somewhat different from that of other nematodes. The adult Strongyloid, always female, buries itself within the wall of the small intestine, depositing the eggs into the lumen of the gut. These hatch out, producing the well known rhabdiform larvae, but the adult worm is rarely seen. In hookworm infection, on the other hand, the eggs rarely hatch within the original host, and the adult worms are much more susceptible to the stupefying effects of drugs and may be washed out of the intestinal tract more readily than is the case with Strongyloides.

The Rivas' plan should be carried out with caution, because superheated solutions are not without untoward effect upon the intestinal mucosa.

RESECTION OF THE KIDNEY*

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AT the beginning of the great renaissance of surgery which followed the discovery of anesthesia and antiseptics, many new fields were opened up and surgeons had to learn by experience what was good and what was bad. It was most natural to imagine that, if disease involved one portion of a vital organ like the kidney, resection of that portion was the best procedure. Nephrectomy itself was a rare operation, and must have seemed very radical. As a result, beginning with Czerny in 1887 portions of the kidney were removed for many different conditions, including stone, hydronephrosis, tumor, tuberculosis, echinococcus, etc. In the early part of this century, Küster was able to review 30 cases. The results were in great part bad, and these bad results were due to faulty knowledge, either of anatomy or of pathology.

FIG. 1. Case 1. Three shadows in right kidney region.

In a few cases it was not realized that the arteries of the kidneys do not anastomose, and portions were removed in such a way that other portions had their blood supply cut off and became necrotic.

Unfamiliarity with the pathology of the kidney was a much more prolific cause of failure. Tuberculous lesions in particular tempted surgeons to resection, but experience soon taught them that the disease often involved portions of the kidney which appeared normal to the naked eye and that nephrectomy was the only suitable procedure. It was also found that neoplasms, apparently of a size suitable for resection, not infrequently had already sent out intrapelvic or intravenous projections which made anything short of nephrectomy impracticable. Among operations for the relief of hydronephrosis resections were recommended both of portions of the pelvis and of portions of the entire sac including parenchyma and pelvis. These operations often failed, as they did not always take into account the necessity for the removal of the causative obstruction, or the inability of the kidney to recover after a certain degree of hydronephrotic atrophy has been reached.

Resection of the kidney, therefore, fell into disfavor, and survived in the textbooks and reference works only for the treatment of solitary benign cysts and localized traumatic lesions.

Quite recently, there has been a renewal of interest in the operation, and with it the realization that there is a very definite and important place for it. The principles underlying the proper use of resection may be expressed as follows: If there is a portion of the kidney so badly damaged that its restoration to normal cannot occur and that its removal is desirable, and if the remainder of the kidney can be shown to be healthy, and to be so located that it will be capable of normal function after the

* From Brady Urological Institute, Johns Hopkins Hospital, Baltimore. Submitted for publication August 28, 1930.

resection, resection may be performed. If the opposite kidney is normal, it is usually not worth while to resect unless at least

Fig. 2. Case 1. Right pyelogram. Shadows concealed by pyelogram.

two-thirds of the kidney can be saved; but if the opposite kidney is for any reason insufficient, preservation of a much smaller amount of functioning renal tissue may be desirable.

Localized renal damage due to calculus provides most of the cases in which resection is being revived. The two writers who have called attention to these cases are Young[1] and Judd.[2] The surgeon is able to do more than merely remove the stone and by eliminating the damaged portion or, as Young puts it, the "stone-bearing area" of the kidney, does something positive and I believe effective to prevent recurrence, particularly desirable when the stone-bearing area is dependent and drains poorly. While resection enables one in such cases to be more radical than heretofore, in other cases it enables one to be more conservative. I refer particularly to cases of double kidney or double pelvis where one-half of the kidney is destroyed by hydronephrosis, infection, or a combination of the two. Many such cases have in the past been treated by nephrectomy, but the good half

Fig. 3. Case 1. Picture taken at time of discharge from hospital showing one shadow in right kidney region.

should and can be saved. My third case illustrates this point. Resection enables such cases to be cured even when the opposite kidney is absent or insufficient. The removal of one-half of a horseshoe kidney also partakes of the nature of a resection, and has been successfully carried out a good many times.

In performing resection the only serious problem is that of preventing hemorrhage. Loss of blood must be avoided during the resection and hemostasis assured at the time of closure. A very careful dissection of the pedicle must be made, and the nature of the vascular supply determined. In certain double kidneys the halves have separate blood supplies. In such cases, the vessels leading to the half to be removed are simply clamped and tied. If there is a single pedicle, as is the case in most single kidneys, the vessels must be compressed during the resection. This can be done by the fingers of an assistant, or by a rubber covered intestinal clamp. Much superior, however, is the method of placing a heavy tape about the pedicle. The tape is then twisted with a clamp until the artery is just occluded.

[1] *Surg. Gynec. Obst.*, 38: 107–111, 1924.
[2] *Ann. Surg.*, 87: 458–471, 1925.

The incisions for the resection are made so that a wedge-shaped piece is removed, simplifying the closure of the kidney. Two

Fig. 4. Case II. Shadows in left kidney region.

rows of mattress suture are placed using a blunt needle and No. 2 chromic catgut. They are tied moderately tight. Any tendency to cut through can be prevented by placing bits of fat and fascia under the catgut. The ends of the outer row of sutures are tied across the incision, drawing its edges together. The pedicle is then released, and further mattress sutures can be placed if found necessary. One should remember that the mattress sutures will cause atrophy of most of the tissue lying within them so that the excision need not be too radical.

I wish to report 3 cases in which resection was carried out successfully. All three illustrate as well interesting diagnostic problems.

Case I. Man aged thirty-four. There had been a sudden onset of pain in the right kidney region, radiating after ten days to the groin and scrotum and accompanied by vomiting. The day before admission there was marked urinary difficulty, which suddenly disappeared with the free passage of about a quart of urine. A few red blood cells were found in the urine, which was sterile. On ureteral catheterization, the phenolsulphonephthalein test showed 13 per cent from the left kidney and 4 per cent from the right. The right ureteral orifice was edematous and inflamed. X-ray showed three shadows in the right kidney region, each about 10 to 12 mm. in diameter and a small shadow

Fig. 5. Case II. Left pyelogram, shadows are concealed by pyelogram. Stone apparently prevents sodium iodide from entering upper portion of pelvis.

Fig. 6. Case II. Small shadows still present after operation. They are probably in the gall bladder.

in the left kidney region (Fig. 1). The pyelogram showed the stone shadows on the right concealed by the shadow of a somewhat enlarged and irregular upper calyx while the shadow on the left was outside the renal pelvis (Fig. 2). At operation a wedge-shaped piece was removed from the upper pole of the right kidney with the idea of obliterating the enlarged upper calyx. The pedicle was controlled with twisted tape, and no difficulty was experienced with the resection, but to my surprise no stones were found even after the most thorough search with a finger inside the pelvis and the other hand outside the kidney. The closure of the kidney was accomplished easily. The convalescence was uneventful and there were no further symptoms. The discharge *x*-ray showed one large shadow in the region of the right kidney (Fig. 3). I believe this patient had passed a small stone and that the opacities seen were extrarenal. Efforts to learn his subsequent history have been fruitless.

Case II. Man twenty-five years of age. He complained of meteorism, belching, anorexia, and pain in the left upper quadrant transmitted to the back. There were no urinary symptoms. The urine, however, showed red blood cells and a few leucocytes, but was uninfected. Gastrointestinal examination and bismuth series were negative. A plain *x*-ray showed a good sized angular shadow in the region of the left kidney with what appeared to be a collection of small round shadows below and external to it (Fig. 4). The phenolsulphonephthalein output was 8 per cent from the right kidney and 3½ per cent from the left. The left pyeloureterogram showed the ureter rather tortuous and four dilated minor calyces in the kidney. The large stone lay in the pelvis at the ureteropelvic junction and extended into the lower calyx, which was the most dilated and which concealed the group of small shadows (Fig. 5). Resection of the lower pole was decided upon because of the supposed presence of multiple small stones which would be difficult to remove completely, and which would probably re-form in the dilated dependent calyx. The resection was completed without difficulty except that first an intestinal clamp and then an assistant's fingers failed to control the pedicle, but a twisted tape was then applied and gave very good results. The large stone was removed from the pelvis. The small stones were not seen. It was thought that they might have been mopped out during the bleeding which occurred before the tape was applied. The closure of the kidney was satisfactory, the convalescence uneventful. An *x*-ray taken later, however, showed the small shadows in the same place they had appeared previously (Fig. 6). Unless the stones had dropped into the depths of the wound, the shadows must represent a calcified gland or gallstones. The gastrointestinal symptoms were completely relieved according to a report received from the patient's physician several months later, and it was impossible to induce him to return to the hospital for further examination.

Fig. 7. Case III. Diagrammatic reconstruction from *x*-ray plates showing atrophic right kidney, left ureter and pelvis of lower half of double kidney, dilated ectopic ureter entering urethra, and dilated upper half of left kidney.

Case III. Reported in another connection.

It was in a woman thirty-nine years of age. She complained of gradual loss of weight and strength, followed by slight fever, pain in the left kidney region, and marked pyuria. Cystoscopic examination showed the urine from both ureters clear and sterile. The right kidney pelvis was small and irregular, and the phenolsulphonephthalein excretion from this side was very low. The left pelvis appeared normal except that it occupied a low position and had only three minor calyces. Repeated research for a third ureteral orifice being unsuccessful and the patient growing worse, the left kidney was exposed and found to be a double kidney, with the upper half convered into a pyonephrotic sac. This sac was drained for three months and the patient restored to health. A pyelogram made by injecting through the drainage tube showed a large tortuous ureter extending down to a point behind the symphysis. Urethroscopy now disclosed the third ureter entering the urethra and Figure 7 is a diagram reconstructed from the various roentgenograms showing the arrangement of the pelvis and ureters. At a second operation the upper half of the kidney was separated from the lower half at the level of a sulcus dividing them. There was some bleeding from the lower half, but not enough to require compression of the pedicle, and it was quickly controlled with two mattress sutures. The vascular supply of the upper half was so diminished owing to infection and hydronephrotic atrophy that it required no special attention, the only ligature being one around the dilated ureter. The recovery of the patient was prompt and complete. She gained 31 lb. and she has been well ever since (two and one half years). In this case resection had to be done, as the lower half of the left double kidney was performing practically the entire renal function, the right kidney being atrophied.

In conclusion, it appears from these cases that resection of the kidney is by no means extremely difficult or particularly risky. In properly selected cases it is very advantageous, and I believe should be done oftener.

COMPLICATIONS OF GONORRHEA:

PERIURETHRAL ABSCESS, STRICTURE, ARTHRITIS*

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THE complications of gonorrhea are so numerous and so varied that adequate consideration of all is beyond the scope of one paper. Were we aiming at completeness, we should include such widely disseminated conditions as simple balanitis, exostoses of the heel, salpingitis and gonococcus meningitis. But we have chosen rather to confine ourselves to 3 of the common complications: periurethral abscess, urethral stricture and arthritis. The statistical clinical data reported here are from the Urological Service of Bellevue Hospital.

Periurethral abscess and urethral stricture must be considered as variations of the same pathological process; periurethritis is the initial lesion in each. Following gonococcus inoculation, the infection soon involves the glands and crypts interspersed between the urethral columnar cells. Adenitis and periadenitis develop. There is swelling of the acini, leucocytic infiltration, increased mucus secretion and partial or complete obstruction of the gland ducts. Resolution without symptomatic evidence of involvement may occur; or if the infection is more severe, the inflammatory reaction intense and relatively extensive, a localized abscess promptly forms. If the abscess is small, it may be asymptomatic and discernible only by careful palpation. On the other hand, it may break its bounds, extensively involve the periurethral tissues and rupture either intraurethrally or externally.

Particularly when there is a mixed infection (streptococci, colon bacilli, anaerobic bacteria) is the development of an extensive periurethral phlegmon (so-called urinary extravasation) likely. It will be remembered that most phlegmons develop in this manner. Although urethral stricture, obstruction or rupture are not prerequisites, one of these lesions will be found in most cases of phlegmon. Except when it directly follows traumatic urethral rupture, periurethral phlegmon or extravasation is always pathologically first a periurethral abscess.

In a recent study of 1538 urethral surgical lesions, periurethral abscess without demonstrable stricture was found in approximately 15 per cent (251). Four-fifths of these had had previous gonorrhea and we believe gonococci to be etiologically associated with the periurethral lesions. While it is usually stated that periurethral abscess is extremely common in the region of the frenum (parafrenitis of Guitterez) we found but 6 instances. In two-thirds of our cases the lesion was found in the bulbous urethra and in one-fourth either at the penoscrotal junction or anteriorly on the ventral surface. Dorsal abscesses occurred but twice. The outstanding symptoms are those of local pain with dysuria.

Periurethral abscesses which rupture externally commonly give rise to urinary fistulae. These occurred in a sixth of our cases uncomplicated by stricture. Except when generalized sepsis develops there is no evidence of functional impairment of the kidneys or architectural renal damage. In 2 fatal cases, however, the blood non-protein-nitrogen was high: 115 and 90 mg. per 100 cc. Both patients died.

The treatment of periurethral abscess depends upon the lesion itself. If there is no evidence of free pus and the lesion is not acutely painful, with skillful neglect it will usually resolve. With the subsidence of the urethritis gentle massage of the peri-folliculitis against a steel sound will

* From the Urological Service of Bellevue Hospital Read before the North Central Branch of the American Urological Association, Indianapolis, Ind., October 24, 1930.

accelerate healing. When frankly suppurative, however, incision rather than wet dressing is indicated. Only rarely will the establishment of intraurethral drainage be found satisfactory. Sometimes this can be accomplished through an endoscope.

Anatomically and pathologically abscess of Cowper's glands is a form of periurethral abscess. We found only 8 cases in this urethral series. Because Cowper's glands are confined between the 2 layers of the triangular ligament, a relatively small amount of swelling will produce great pain. As a rule, the diagnosis is easy; palpation with the index finger in the rectum and the thumb on the perineum will indicate the presence of Cowper's gland involvement. The commonest diagnostic error is the interpretation of Cowper's abscess as ischiorectal or prostatic abscess. The treatment is surgical in most cases. Extension of the abscess may terminate in intrapelvic or perineal phlegmon.

Following either surgical or non-surgical treatment of periurethral abscess, considerable periurethral sclerosis is likely to form with the ultimate development of clinical stricture. In order that stricture does not develop, it is highly important that urethral dilatation be carried on for some time following apparent cure of the abscess. In a series of 340 stricture cases which had been operated upon previously, 29 or approximately 10 per cent had been operated on for periurethral abscess. In a larger series of 1244 strictures,[1] periurethral abscess co-existed in 15 per cent (188). In this larger series, palpable periurethral nodules of infiltration were found in an additional 15 per cent. In other words, in nearly a third of stricture cases, palpable periurethritis exists.

It is apparent therefore, that the likelihood of stricture formation must be remembered and its preventative treatment becomes a prime consideration in the proper management of periurethral abscess. It is indeed secondary only to evacuation of the pus.

We must now return to the pathology of gonorrheal periurethritis. Unless periurethral abscess develops, the inflammatory lesion may resolve and leave no discernible scarring or it may heal by sclerosis which ultimately becomes evident as stricture. With sclerosis a certain amount of infection is encased in the inflammatory scar and adjacent urethral glands. A vicious cycle is thus induced in which the persistent infection stimulates more scarring with stricture increase. Acute congestion from sexual excitement, the passage of instruments or alcoholism often stimulates the smouldering infection to renewed activity. This is manifested by urethral discharge, sometimes pain at the stricture site, sometimes an intensification of the urinary symptoms and not infrequently the development of an acute periurethral abscess superimposed on stricture. With more widespread periurethral involvement, phlegmon or so-called urinary extravasation develops. In a recent study of 135 cases[2] of periurethral phlegmon we found stricture to be the primary surgical lesion in 114. Twenty of these patients had been previously operated upon for stricture.

Renal damage secondary to stricture gives great concern in some instances. In (198) approximately 15 per cent of our stricture cases the two-hour phenolsulphonpthalein output was less than 30 per cent. In 3 cases no dye was excreted and in 4 cases but a faint trace. With the exception of the immediate treatment of the acute suppurative complications of stricture (periurethral abscess and phlegmon) the fundamental therapeutic considerations are quite identical with those of prostatism. The ultimate establishment of free drainage is the keynote of successful treatment.

It was recognized over three centuries ago by John Read that the proper management of the acute gonorrheal urethritis

[1] Campbell, M. F. Stricture of the male urethra. *Ann. Surg.*, 89: 379–399, 1929.

[2] Campbell, M. F. Periurethral phlegmon (extravasation of urine). *Surg. Gynec. Obst.*, 48: 382–389, 1929.

is the best preventative or prophylactic treatment of stricture. It is well known that the development of stricture is largely dependent on the severity and intensity of the infection but it seems to be less generally appreciated that not infrequently stricture is directly the result of improper treatment rather than the infection. Local under-treatment therefore, is preferable to over-treatment and to quote Keyes "the man behind the gun is more important than the solution of it." While most strictures are not manifest until months or years after the gonorrheal attack it should always be borne in mind that they may develop within as short a period as four weeks and, passing unrecognized, infinitely delay the cure of the urethritis. Of 714 patients who had had but one attack of gonorrhea, in approximately 4 per cent did stricture of sufficient degree to bring the patient to the hospital develop in less than one year after the onset of the infection. In about 12 per cent, a similar condition developed in less than two years. In 40 per cent, (299) the patient did not seek treatment for stricture for fifteen years or more following the infection.

The non-operative treatment of stricture is persistent and prolonged dilatation with steel sounds; we are aware that some surgeons prefer the Kollman dilator. This dilatation brings about resorption of the inflammatory exudate and will cure a few. By this method all strictures can be controlled; formed scar can be removed only by excision. As long as a stricture shows evidence of contraction it is not cured.

The site of stricture offers suggestions as how best to treat it. When at the meatus, it should always be cut. While well formed stricture of the pendulous urethra more frequently requires cutting as well as repeated dilatation, stricture of the bulb unless complicated by active periurethral infection usually responds well to dilatation alone. Strictures of the membranous urethra rarely follow gonorrhea; they are usually due to trauma. The diagnosis of membranous stricture is difficult and because incision will probably injure the external sphincter, dilatation by sounds is the better treatment. Often impassable strictures become passable with rest and Sitz baths. If they do not, they must be cut.

Of our stricture series a third were not operated upon at the time of the first admission to the hospital. They were referred to the out-patient department where more or less continuous regular treatment by sound dilatation was carried out. Some of these showed no response to dilatation and were referred to the hospital again for operation. Therefore, failure to respond to dilatation is a definite indication for operation.

Unquestionably a great many of our patients who were operated upon might ultimately have responded satisfactorily to dilatation alone. But for economic reasons and because so many of these patients are neglectful, the immediate attainment of a maximal urethral caliber by operation seemed the wisest course. On the other hand in private practice with a more intelligent class of patients urethrotomy need be but rarely employed.

Gonorrheal Arthritis is the least frequent of the common complications of gonorrhea. The incidence varies from 2 to 4 per cent and most often attacks males. More recent studies have conclusively shown that contrary to older teachings gonorrheal arthritis is a polyarticular rather than monoarticular metastatic lesion; in two-thirds of our cases at Bellevue more than one joint is involved. Furthermore, a joint once involved is most likely to be the site of future arthritic lesions if urethral reinfection occurs. Trauma and unusual joint activity definitely predispose to gonococcus arthritis. In hospital practice the incidental ratio of lower to upper extremity involvement is 4 to 1. The lesion most often appears during the second or third week of the urethral infection. The symptoms of local pain and other evidence of inflammation together with

general systemic manifestations of toxemia, fever, sometimes nausea and vomiting, are well known. When arthritis occurs in association with active gonococcus urethritis the diagnosis is easy; when gonococci are not demonstrable greater diagnostic difficulties are encountered.

Our greatest interest focuses on treatment. The large variety and number of therapeutic methods advocated at once indicate that there is no thoroughly satisfactory treatment. Therapeutic attacks have been directed against the local joint lesions, against the active primary focus and also against the body as a whole. This latter method attempts to employ immunologic reaction by the injection not only of gonococcus vaccines but of other bacterial vaccines, immune serum, or foreign protein, as well as by autohemotherapy and autoserotherapy. Chemicals such as acriflavine, mercurochrome, metaphen, calcium chloride, sodium iodide and iodine (Pregl's solution) have all been used with discouraging results. Attacks against the active local infection in the urethra, prostate, and seminal vesicles have also proved inadequate. It would seem that the best immediate results have been obtained when treatment is applied directly to the involved joint. Such treatment includes immobilization with subsequent active or passive motion, heat, diathermy, roentgentherapy and even surgical aspiration or exposure.

A short time ago Wehrbein[1] made a most comprehensive study in 610 cases of gonorrheal arthritis admitted to the Urological Service at Bellevue Hospital over a four-year period. During this time practically all of the aforementioned therapeutic agents were employed and the results obtained are here briefly reviewed.

A fourth of these patients received no treatment other than rest in bed, catharsis, and nourishing food. Obviously they were the milder cases; the hospitalization period averaged 7.9 days, in counter distinction to the general average of 18.6 days of all arthritic cases. Vaccines were used in nearly half of the entire series of 610 cases, were given subcutaneously, intramuscularly and in some cases intravenously at intervals varying from three to eight days. The initial doses were small (5 to 25 million) but were gradually increased so that a few patients received as much as one billion at a time. In this series the results were unsatisfactory. Many were rendered temporarily acutely ill and a few felt somewhat improved during the three or four day convalescence from the vaccine shock. A striking vaccine immunity was obtained by many but this did not serve to cure the arthritis. Some patients who had received vaccine treatment elsewhere refused it when admitted to Bellevue.

Similar unsatisfactory results were obtained by the use of foreign protein (typhoid vaccine, casein, whole milk, fluid from the involved joint, and autogenous blood). In many cases an alarming systemic reaction occurred during which time the patient thought little of his arthritic symptoms; invariably these were again complained of in three or four days.

For intravenous chemical injection mercurochrome, metaphen, and Pregl's iodine solution were used. The injection of the latter accomplished nothing. Metaphan exhibited no therapeutic effects. Mercurochrome was given to 14 patients in 1 per cent solution, the dosage being 3 to 5 mg. per kilogram body weight. One to five injections were given each patient and while no serious permanent effects were observed, a marked generalized systemic reaction with sometimes vomiting and albuminuria occurred in a few. Mercurochrome was the only medication given which had any demonstrable beneficial effect. The hospitalization period of these cases was but one day less than the total average (eighteen days).

Direct attack on the local genital infection was of no therapeutic value. It is of interest in this connection that in 4 of the group of 30 cases treated solely by this

[1] Wehrhein, H. L. Gonococcus arthritis. *Surg. Gynec. Obst.*, 49: 105, 1929.

method a severe systemic reaction with high temperature followed prostatic massage. In 3 cases Pregl's iodine solution was injected into the seminal vesicles without benefit.

Therapeutic attack directed at the joint itself offers the greatest hope of symptomatic relief for the patient. In the acute stage this is best accomplished by the application of a plaster of Paris cast sufficiently snug to immobilize the joint. This method was followed in 144 patients; the casts were left on an average of ten days, were renewed in 15 cases, and in only 7 instances were joint symptoms aggravated by the splint. This latter finding suggests improper splint application with the oint in an uncomfortable state of flexion.

Great care should be observed that immobilization be not carried on too long as muscular atrophy and joint immobility become more marked. The best results apparently have been obtained by the use of the hot tub bath as soon as the condition of the patient will permit transportation. In the hot water active motion can usually be carried on quite painlessly, and is believed to result in fewer ankylosed joints. Unfortunately at Bellevue we have been unable to carry out this treatment. Application of heat to the joints, passive and active motion, and massage of the atrophied muscle hastens restitution to normal.

Next to joint immobilization by plaster cast, deep *x*-ray therapy applied to the affected joint has afforded most prompt symptomatic relief. Twenty-two of twenty-seven patients so treated were relieved by one treatment. Only 3 were unrelieved by a series of 4 exposures. The roentgenologic effect is local and will be noted only in the joint to which it is applied. A small dose (10 to 25 per cent of skin erythema with copper and aluminum filters) is cross fired at the joint. The therapeutic action of these rays is little understood in these cases but it would seem that the endothelial, fibroblastic and leucocytic repair elements within the joints are stimulated by the relatively small therapeutic dose.

At the present time therefore, while there is no specific treatment for gonococcus arthritis, the immediate relief of local symptoms is best accomplished by splint immobilization of the joint or the application of a partial erythema dose roentgen-ray exposure. A useful joint will be rendered more likely if active or passive motion is instituted relatively early.

In a rather extensive experimental therapeutic study on the Bellevue Urological Service mercurochrome intravenously was the only therapeutic medium which by injection was found to possess any merit. Observation of the reaction following the use of this drug in many cases would, I am sure, cause one to hesitate in submitting to its use on himself. Vaccines were uniformly without therapeutic value. Rarely does joint suppuration occur and when it does, arthrotomy is usually indicated.

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MANY things have been used in the past with which to tie silkworm gut, mostly with the idea of preventing the cutting of skin and subcutaneous tissues, without much thought of holding in apposition and fortifying the fascia. Some of the things used have been long and short folds of gauze, buttons, dental rolls, glass rods and rubber tubing of various kinds, sizes, etc.

In my efforts in the past to prevent postoperative hernia, also to produce a narrow, well-approximated wound, with as little fibrous tissue scar as possible, originated the fascia anchors, after I had tried many of the things heretofore mentioned.

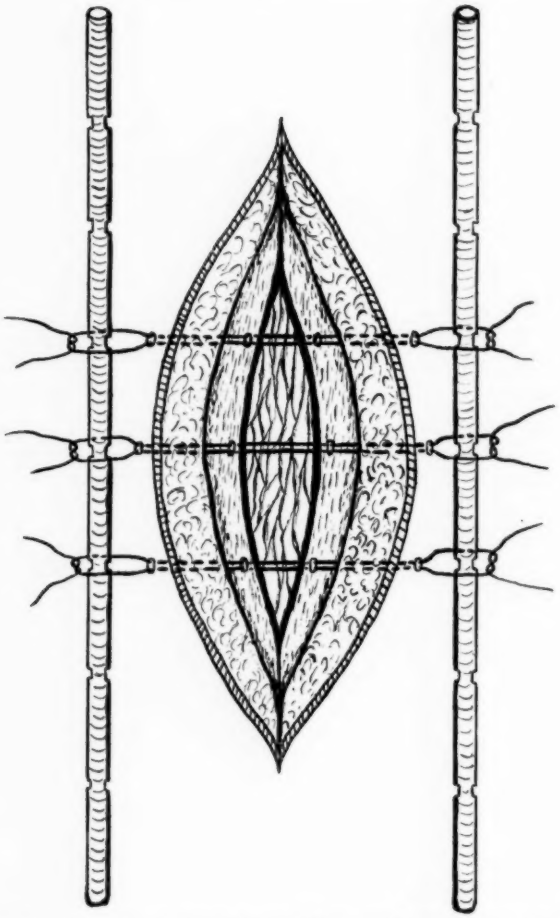

FIG. 1. Fascia anchors in position, with double strands of silkworm gut ready for tying.

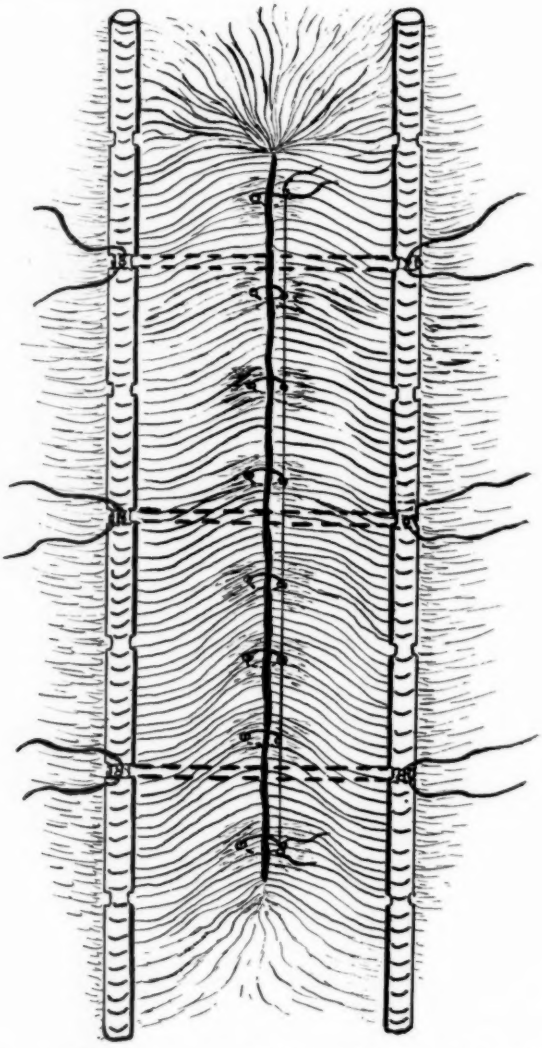

FIG. 2. Silkworm strands tied. This gives splendid apposition of incised layers with elevation.

DESCRIPTION

The fascia anchors are made in various lengths, but those commonly used are the 10 cm., 16 cm. and 20 cm. lengths. Diameter 4 mm. They are grooved to prevent the sliding of silkworm gut, each space between grooves measuring 2 cm., and are made of rustless steel, chromed.

* Submitted for publication October 27, 1930.

The anchors may be used to measure the size of any pathological growth, length of incision etc., as well as for fixation of silkworm gut, to bring into close apposition the fascia layer, particularly of the abdominal wall; also in the closing of a wound following a radicle mastectomy and in any other part of the body where silkworm might be used.

ADVANTAGES

A wound is easily cared for with the fascia anchors in place and the surgeon may use any technique in cleaning wound when changing dressings, as there is no absorption of serum or purulent discharge, as in the gauze, rubber and other things used, which cause foul-smelling conditions.

The fascia anchors eliminate dead space of wounds, air bubbles, assist in hemostasis, better apposition of wounds, with less fibrous tissue scar, aid in preventing postoperative wound opening, due to strain, etc.; they also help to prevent postoperative hernia.

It is not necessary to place silkworm tight enough on fascia anchors to produce necrosis. The anchors prevent the cutting into tissue that so often occurs when tied over incision, causing discomfort to patient and aggravating the wound, increasing the tendency toward infection.

TECHNIQUE

There is nothing mysterious about the use of these fascia anchors. The surgeon may use ordinary silkworm, as he does in his everyday method to close the wound,

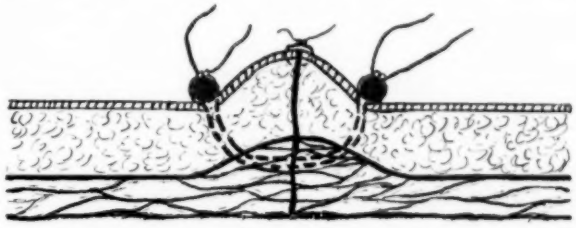

Fig. 3. Transverse section of Fig. 2. Silkworm strands pass through skin, subcutaneous tissue and fascia. Marked approximation gives less scar tissue as end-result.

using two strands in each needle, in place of one, grasping the free ends with hemostats. The fascia anchors are passed between the double strands on each side, tying one side, then the other, tying first the middle double strands, following with proximal and distal strands. If the strands are carefully tied with gentle approximation of wall layers, a splendid apposition will be brought about, with slight elevation of incision between the anchors. Gauze may be placed below each end of fascia anchors to prevent pressure, and the gauze changed with dressing by gently lifting the anchor ends with mousetooth thumb forceps or Allis clamp.

It is advisable to use the fascia anchor just a little longer than incision, as the pressure is much better equalized. Two to three centimeters are a good distance to place fascia anchors laterally to incision.

INDICATIONS FOR EXCISION AND GASTRECTOMY AND RESULTS FOLLOWING OPERATION*

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CHARLOTTE, N. C.

CASE I. In July, 1917, before going into military service in September, we did a palliative gastroenterostomy, merely to relieve obstruction, in a man fifty-two years old who had been vomiting persistently, had lost over 50 lb. in weight, was pale and almost entirely exhausted. There was a mass, not only felt but seen in the epigastrium and right hypochondrium. He vomited food and barium of the day before and showed by *x*-ray studies a very large stomach with a little barium passing into the duodenum and an irregular outline of the antrum, a crater, the apex of which was along the lesser curvature at the pyloric canal. At operation there was a mass the size of a lemon in the antrum up to the pyloric canal, with the cap of the crater toward the lesser curvature. The exploration was quickly terminated with a gastroenterostomy. A diagnosis of cancer with metastatic lymph glands was made. The patient never vomited again, greatly improved and gained weight during three weeks in the hospital. My good-bye to him when he left the hospital was a final one and with more feeling than he ever suspected. Two years later after the war this same man, in the bloom of health and a gain of 60 lb., returned to see me, to thank me for curing him. There was no mass to be felt, *x*-ray studies showed a rapidly emptying stomach of normal size and the barium passed out both by the pyloric canal and gastroenterostomy opening. The man is still living and well and has paid little or no regard to his diet since three or four months following his operation.

In the light of nowadays I should have felt a confidence in his outcome, if I had considered the location of the ulcer and had made a frozen section of one of the lymph glands along the lesser curvature. Almost every surgeon I have talked to, has recited a similar surprising experience.

CASE II. In March 19, 1924 a man aged thirty-three was rushed to the hospital on account of having been struck with violent pain in his right upper abdomen and right side. He doubled up with severe pain and rigidity of his abdomen, which he in no way relaxed until he was under full anesthesia. This was Wednesday afternoon and he had just been dismissed from the hospital Monday after the third Sippy treatment of eight weeks each and had eaten nothing but eggs, milk and very light cereals. There was considerable fluid in the right hypochondrium and a hole nearly the size of a ten cent piece and an indurated area the size of a dollar on the anterior surface of stomach extending to the lesser curvature. There were enlarged glands along the lesser curvature. For two reasons the indurated area was excised with a cautery, first to gain more supple tissue for enfolding and second to get rid of the widespread lesion. A considerable section was thus removed and when wound was closed the antrum was very much narrowed and the pyloric canal encroached upon. With compress in the hypochondrium and change of gowns, gloves and instruments a gastroenterostomy was done. The wound healed per primam and the patient made an uneventful recovery taking a full diet in two months. He has not had the slightest complaint in over six years. Figures 1 and 2, Case II, show the stomach during his last Sippy treatment with the ragged area located in the antrum, near the pyloric canal and a small crater continuous with the lesser curvature and four years later a narrow antrum with serrated outline along the lesser curvature. Practically all of the barium is passing through the gastroenterostomy opening.

After these resections of either gastric or duodenal ulcers with gastroenterostomy or pyloroplasty it is almost impossible to draw any conclusions from *x*-ray studies beyond the proper emptying of the stomach and possibly the absence of a definite crater. Compare Figure 3 of a resection of duodenal ulcer and pyloroplasty.

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Case III. May 21, 1924 a woman aged sixty-seven who for years suffered such violent pain and nausea on taking food, occasionally relieved by washing out the stomach, but as frequently requiring morphine, begged for relief by operation. She knew and was repeatedly warned that her general condition, rheumatism and leaking heart, already twice decompensated, made her operation a risk. She preferred the risk and death even, to life as it was. *X*-ray studies showed a collar button crater from the posterior surface of stomach in the upper part of the corpus and near the lesser curvature. This crater was a fixed point and did not shift with the movements of the stomach. The lesion did not show at all in a first series of *x*-rays and was only brought out on placing the patient in the oblique position (Fig. 4).

Fig. 1. Case II. Stomach during last of three Sippy treatments with ragged area located in antrum, near pyloric canal and small crater continuous with lesser curvature. This ulcer perforated.

The operation was done with local anesthesia and gas. The ulcer was found on the posterior surface of the upper corpus, intimately attached to the pancreas. The fixation to the pancreas and the drag down upon it, as well as the inflammatory reaction of the ulcer evidently caused the severe pain. There were enlarged glands along the lesser curvature. Access was easily made through the gastrohepatic omentum, the ulcer crater separated from the pancreas, the pancreas gently cauterized and closed with catgut sutures. The ulcer resected and stomach closed. At this stage of the operation and without warning save for the risky heart condition, the patient's heart gave way and she died shortly after the abdominal incision was closed. Pathological section of the ulcer and gland showed no malignancy.

Fig. 2. Case II. Four years after cauterization and closure of ulcer and gastroenterostomy. Narrow antrum with serrated lesser curvature. Most of barium passing through gastroenterostomy opening, showing necessity of gastroenterostomy after resection of ulcer.

Case IV. A man sixty-two years old, March 25, 1922, who had dyspepsia and colitis for twenty years. *X*-ray pictures taken several years previously showed gastroptosis and slow motility; more recent examination of gastric contents showed absence of hydrochloric acid. There was more and more gastric distress and all foods disagreed with him. *X*-ray studies revealed a small stomach with feeble contraction waves, marked reduction of cavity, ragged outline of antrum along the greater

curvature. The man was losing rapidly in weight and his color was bad. At an exploratory operation, the walls of the whole antrum and just had a voluminous gastric hemorrhage. *X*-ray studies in the man failed to disclose a definite lesion. At operation on both patients

FIG. 3. Duodenum and antrum after excision of duodenal ulcer and Finney's pyloroplasty. Case symptom-free but nothing to be gained from study of contours.

FIG. 4. CASE III. Collar button crater from posterior surface of stomach in upper part of corpus, near lesser curvature. Shown only in oblique position. This crater was fixed to pancreas, did not shift with movements of stomach and caused unbearable pain.

corpus were thickened and hard, the picture of the so-called leather bottle stomach. There were no glands. After the exploratory operation he was seen in consultation with Drs. Kelly and Burnam who advised radium and *x*-ray and Dr. Finney who suggested the possibility of a total or subtotal gastrectomy. The patient chose the easier and useless route of treatment with *x*-ray and radium. He rapidly reached the point where he could not be fed by mouth on account of extreme gastric distress and aversion to food. For the purpose of feeding a duodenostomy was done and in this way he was fed until he died. Conditions of living could not have been worse for him if a gastrectomy had succeeded and if he had died, he would have been relieved of months of suffering and a useless life.

CASES V and VI. Two cases, one of a man sixty-four years old, Jan. 8, 1921, the other a woman sixty-nine years old Jan. 30, 1924. Both complained of gastric distress, both had lost weight, the man, 42 lb.; the woman had

there was found an indurated area the size of a dollar in the anterior wall of the antrum, with a large shallow crater. In the woman the induration extended up to and embraced the lesser curvature; in the man, neither curvature was involved, the lesion was nearer the greater curvature. In both cases there were a few glands along the lesser curvature near the pyloric canal. A gastrectomy with resection of the whole antrum, about half the stomach, was done in both patients. Pathological section in the one case, the man with the ulcer frankly and freely on anterior surface of the antrum showed malignancy; in the other case, the woman with the ulcer nearer and embracing the lesser curvature showed no malignancy. Both patients are living and well, the woman after six years, the man after nine years. Since two months following their operations both have eaten practically a full diet, have regained weight and color and have no gastric distress. *X*-ray studies following gastrectomy show the stomachs while somewhat reduced

in size, still capable of accommodating themselves to the intake of a full diet and a corresponding restoration of the patients to their

Fig. 5. Stomach following gastroenterostomy between duodenojejunal angle and stomach for obstruction of duodenum and stomach where emptying time is much too fast. Compare with Fig. 6.

normal weight and color. The resected stomach exhibits a motility just as vigorous as that following about 30 per cent of gastroenterostomoies. Emptying time less. Compare Figures 5 and 6.

Out of 9 cases where gastrectomy was done, 7 patients are now living and well, 2 are dead after fourteen and eighteen months respectively from metastasis. Even the two patients dying of metastasis and cachexia were able to take their meals with comfort and died without any abdominal distress.

Cole reports 26 cases of ulcer of the corpus gestrica where 11 patients were treated with gastric resection, 10 with excision and 5 with gastroenterostomy without excision. Of the 11 treated with gastric resection 6 lived to leave the hospital and 5 died while in the hospital. Of the 10 treated with excision; 2 were mucosal ulcers and 1, as proved by microscopic

Fig. 6. Stomach after gastrectomy, where more than half of the stomach was removed for carcinoma and the Pólya type of anastamosis was done. Emptying time far less than gastroenterostomy. Stomach accommodated full meals without discomfort. Compare Fig. 5.

examination, was already a healed ulcer. Of the remaining 7; 2 died, 2 were worse, 1 was improved and 2 were said to be improved. All of the 5 cases treated with gastroenterostomy lived but as we can compare each of these with a similar case treated medically without gastroenterostomy, the question arises: did the ulcer heal because of the gastroenterostomy or in spite of it. Cole's conclusions are as follows:

1. We must study each regional type of ulcer separately and therefore this communication has been confined to presentation of corporic ulcers.

2. Mucosal ulcers are so superficial and

transitory that they should not be included in a consideration of whether or not to operate.

3. If an ulcer has distorted a stomach almost beyond recognition such a distortion becomes a complication and that case is definitely surgical. No case of this character is included in the 26 cases presented herein.

4. Ulcers that occur nearer the greater curvature than the lesser should be considered ulcerations in carcinomatous areas and not benign ulcers.

5. Any ulcer that increases in size, after the initial avulsion of the crater, should be considered malignant, or at least not a single or benign type of ulcer. This increase in size must be determined by comparing roentgenograms made at the end of one week in bed, two weeks in bed, and if necessary at the end of a third week in bed, care being taken to observe that the patient is in the same posture during each examination.

6. The mortality of gastric resection for ulcers of the corpus is so extremely high that this procedure is not justified as a method of treatment for corporic ulcers.

7. Excision of a small ulcer high up on the corpus may be successful. Excision either with cautery or knife, of an ulcer near the sulcus angularis is contraindicated as it usually results in a gastric deformity requiring subsequent surgical procedure.

8. Gastroenterostomy for corporic ulcers is merely an excuse to do something. These ulcers heal in spite of the gastroenterostomy rather than because of it.

9. From an analysis of these facts, it is evident that surgical procedure is definitely contraindicated in all cases of corporic ulcer and that it should be resorted to only in such cases as are known to have gradually increased in size during a three weeks' period of rest in bed under roentgenologic control or which in that same period of time have definitely failed to diminish in size. In this latter group of cases, surgical procedure should only be resorted to, however, in the event that the symptoms are so severe that the patient demands operation. In these cases, it must be borne in mind that the same constitutional conditions which prevent the healing of ulcers, such as arterial sclerosis, make the patient an unfavorable surgical risk.

I am persuaded that Cole's observations and conclusions from the point of view of a roentgenologist are accurate and cogent and that they can be applied practically in the determination of not only whether to operate or not but what operation to do. It seems to be a fact that almost all ulcers may be classified as corporic, prepyloric and postpyloric ulcers and that they occur in the ulcer-bearing area along the lesser curvature. Ulcers in these locations are inflammatory and not malignant. Ulcers elsewhere in the stomach, particularly near the greater curvature may be malignant and must be considered as such.

When such ulcers extend to enormous size, as they sometimes do, so as to produce lameness and obstruction of the stomach, as in the case first cited (Case I) there is no other alternative except to give relief of obstruction by gastroenterostomy; and in an ulcer of such size the difficulty and uncertainty of determining its original location and whether or not it be malignant may be impossible. The diagnosis may be aided by a frozen section of one of the glands. Doubt as to the diagnosis may still remain and force the question of gastrectomy. It is generally accepted from experience in the hands of most operators and proved by postoperative *x*-ray studies that "v shaped" resection and "Sleeve" resection too frequently leave a deformed stomach with mechanical function interfered with. This is particularly true when resections are done along the lesser curvature near the sulcus angularis. In these cases, a gastrectomy is preferable. When ulcers are located outside the ulcer zone, that is, not in the antrum along the lesser curvature, excision is indicated, because of the possibilities of serious trouble inherent in the ulcer, namely perforation: (Case II. Mr. S.; hemorrhage, Case VI., Mrs. S.; deformity with perigastric adhesions; Case IV., Mrs. Sholtz; narrowing of lumen by presence of mass and cicatricial contraction; and most important malignant degeneration; Case V. Mr. R.).

In these cases, the large obstructing ulcer at the pylorus along the lesser curva-

ture healed under gastroenterostomy; the perforated ulcer on the anterior surface of stomach under resection and gastroenterostomy; that on the posterior wall, adherent to the pancreas, was resected; in the 2 cases, one of the woman with hemorrhage and the other of the man, the ulcers were located in the antrum on the anterior wall on which gastrectomy was done. The choice between resection and gastrectomy is determined largely by the amount of the wall to be resected and the resulting deformity and interference with motor function. Where such a large area is to be resected gastrectomy is preferable; also where the ulcer is located outside "the ulcer bearing area" and where the chances of malignant changes are far greater, gastrectomy is indicated. Finally and in repetition the question of operation and what operation is determined as follows:

I. Ulcers of the antrum and pylorus along the lesser curvature and duodenum are benign and frequently heal under medical treatment. Dangers are perforation, hemorrhage and obstruction.

II. Ulcers on the gastric side of the pyloric canal and outside the "ulcer bearing area" may or may not be malignant. The possibility of malignancy requires excision or gastrectomy.

III. Excision for malignancy should be wide and extensive and should therefore be extended into gastrectomy.

IV. The function of the stomach following gastrectomy is comparable with that following gastroenterostomy and superior in every way to that following "v shaped" and "Sleeve" resections.

STRAINS AND SPRAINS*

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IN the fields of orthopedic and traumatic surgery there are two very common injuries, the strain and the sprain, which present themselves separately or together for consideration. Although these types of trauma are distinct and different entities, they are not sufficiently considered as such. In fact such injuries are unfortunately not separately identified, and the result is that the expression designating a strain or a sprain means nothing very definite by way of visualization in the minds of many.

Of course, the laity does not need to know the distinction between the entities, and they use the terms with the most vague realization of what they typify. To them, the analysis for the correct application of these terms to lesions is unnecessary. With the orthopedic and traumatic surgeon, the differences between a strain and a sprain must be fully realized. And since there are for each, separate considerations, these entities will be somewhat fully discussed. The words, strain and sprain, are entirely too commonly considered as synonyms. They are used interchangeably when it should be realized that each should express a distinct lesion, but which is which, does not often seem worthy of the user's time to investigate. One or the other word is used very commonly at present in the hope that with the injury being considered, the word used to designate same implies everything which is found.

A strain and a sprain are two distinct lesions, which as such are very ordinarily first and often last seen by the patient or the family. Commonly either such lesion causes little concern when mentioned merely as a strain or a sprain. However, we all have seen serious consequences result, because either lesion was improperly considered as requiring experienced handling.

DIFFERENTIATION OF STRAINS AND SPRAINS

STRAINS

DEFINITION: A strain is an overstretching or an over-exertion of some part of the musculature. Strain implies a call for usage of some muscle or muscle group beyond that which normal tone has usually supplied.

LOCATION: Strain may be identified in any portion of the musculature. It is most commonly found in the muscles of the extremities and the back. There are no muscles, with voluntary function, which are not subject to strain. There is no bone or joint injury in strain, as such.

SPRAINS

DEFINITION: A sprain is a severe wrenching or twisting of a part attached near or around a joint. It implies a resultant trauma, very commonly a fracture-tear or chipping-off of some of the bone to which the soft parts are attached. It may, however, be only the tearing of the ligamentous or tendinous structure of muscle, which is nevertheless a matter for serious consideration.

LOCATION: Sprain is, as the definition implies, in or around the joint. The commonest sites for sprain in their approximate order are, the ankle, fingers, wrist, knee, elbow, hip and vertebral column. It implies ordinarily a joint injury with an interruption in the continuity of ligamentous or tendinous insertions around a joint or of the bones entering in the joint.

* Read before the North Side Medical Society. Submitted for publication December 4, 1930.

Strains (*Cont.*)

Symptoms of Strain (Subjective): Among athletes, in opening training or during the breaking-in period, strain manifests itself as the general muscle soreness and stiffness termed "Charlie-horse." There are as subjective symptoms, soreness, stiffness, tenderness on palpation, pain on motion, weakness and frequently swelling in the muscles involved. These disturbances do not, as a rule, manifest themselves until about twenty-four hours after the overstretching or over-exertion of the parts, and by this time they will have become very acute. They will continue so for from forty-eight to seventy-two hours in spite of all treatment, other than rest. However, at the end of this time, there follows a gradual subsidence of the symptoms, and the amelioration permits of mild function.

Objective: The general findings are negative for the examiner without handling of part. There are no unfavorable sequelae from unattended strain. The symptoms of strain are always gradual and sneaking with the onset, there being no history of a severe injury bringing about the same. Frequently, an unwarranted fall will cause a general evidence of strain in the non-athletic type.

Pathology: in case of strain is that of engorgement and congestion from over-use or overstretching of the part. This implies an increased flow to and an impeded flow from the part of the blood in the vessels supplying same. There are, consequently, distentions and rarely ruptures of the smaller or capillary vessels. Upon the discontinuance of the overstretching or over-exertion there is a readjustment of the circulation, and an arrest of further damage to the musculature is the favorable result. An edematous result, a swelling of the part occurs from the over-distention due to congestion of the vessels. The consequence of this effort is a leakage of serum from the vessels, or a possible rupture of the capillaries with hemorrhage or extravasation of blood in the area

Sprains (*Cont.*)

Symptoms of Sprain (Subjective): They are mild and severe. There may be an initial attack of mild shock or syncope. Nausea and vomiting are not infrequent. Sudden sharp pain around the joint involved in the injury, impaired function is at once evident. Cessation of pain during rest with a possible feeling of fulness, throbbing with tension. With efforts to movement there is stiffness of the joint involved, which increases as time goes on, with injury unattended. This is due to effusion of fluids in and around the joint.

Objective: Swelling is an early sign and if there is much injury to the soft parts there may be discoloration due to extravasation of blood in the tissues. There is great pain during manipulation, extensive tenderness around the entire area involved. *X*-ray will commonly detect a fragment, sliver, or shell of bone separated completely or incompletely from the parent bone. It should be made known to the subject at once, that unsupported or unattended sprain is a serious issue, which if let alone may become a dangerous problem. The symptoms of sprain are always acute in their onset, there being distinct history of severe trauma.

Pathology: of sprain is generally the same in any location. Inasmuch as there is a tear to or around the joint we should expect to find a separation or interruption of continuity or structure with extravasation of fluids, such as serum, fibrin, synovial fluid and blood, at and around the immediate location of the trauma. There is, consequently, extensive infiltration in the surrounding soft tissues with fluid, coming from the muscle fibers being swollen, some ruptured and others necrotic. The bony fragments torn from the parent bone in sprain remain attached to the overstretched and torn ligament or tendon. From both surfaces or ends included in the tear there is effusion which becomes more abundant during use. The interstitial tissue between the muscle fibers around

STRAINS (*Cont.*)

involved. A strain, rarely as such presents further serious pathology and a reestablishment of the circulation usually restores the tissues to normalcy.

DIAGNOSIS DIFFERENTIAL: of strain from sprain might be problematical, although it is believed that no other type of injury should easily be mistaken for it. Strain is a simple injury with no history of a serious accident or trauma to a part leading up to the incapacity. Strain occurs with sprain, dislocation, or fracture, but it is never treated separately as a complication. When it occurs alone it is a condition with no serious interruption or impairment in the continuity of structures, remains acute for several days, and disappears gradually with or without treatment.

PROGNOSIS IN STRAINS: always good whether treated or not. The old system of rest to the part is not generally to be advised for rapid recovery. However, in the older patients, this form of treatment, because of possible protracted favorable prognosis, is often advisable, and this is more especially the case with women.

TREATMENT OF STRAINS: is always meted out with a full consideration of the individual's habits. Ideally in the young, and the old of athletic tendencies, the use of the strained part should continue. This however, must be moderated with caution during the lighter normal activities. Liberal massage is very helpful, and free manipulations (active and passive) of the affected part are advised. For massage, alcohol, olive oil, witch hazel or any of the host of rubber's pet lotions or liniments may be

SPRAINS (*Cont.*)

sprains shows blood stream and lymphatic activity early at work to overcome the broken part.

DIAGNOSIS DIFFERENTIAL: of sprain from strains, fractures and dislocation is a matter stressed by some authorities. Naturally with the history of an acute injury, strain can easily be ruled out, although it will come up commonly as a complication of sprain. A sprain is in reality a tear or fracture-tear around a joint of insufficient severity to interfere with general contour, alignment and articulations of the bones. The reality of a sprain being a severe injury develops the fact that, as a tear or fracture-tear, a sprain commonly merits fracture consideration for treatment. Sprains are diagnosed from the history of injury, the force or method producing same, the lack of change in general contour of the part injured, history of ability to use part for a time, no evidence of displacement, and general appearance of part, as well as, conduct of patient. The *x*-ray is very helpful with the diagnosis of sprain involving much or little of the bony structures.

PROGNOSIS IN SPRAINS: guarded, unless properly treated. If improperly handled severe damage, such as ankylosis, periostitis, osteoperiostitis, myositis, osteomyelitis, pressure neuritis, impairment of function and deformity may result.

TREATMENT OF SPRAINS: is much the same as in the treatment for fracture. Placing the part immediately at rest minimizes the severity of the symptoms. A sprain requires the placing of the part in a position which is that of over-correction with comfort to the patient. This position must be maintained by immobilization with light splintage, plaster-of-Paris being the dressing of choice. Where the severer symptoms manifest themselves, temporary splintage on a board or with any apparatus

Strains (*Cont.*)

used. Where there is extreme pain during the early onset of the condition, allonal or morphine will ameliorate the symptoms.

Convalescence of Strains: is rapid with massage of the muscles involved. The early use of the affected part is to be encouraged. It should be remembered by all means that moderate normal use, although painful in the start, is safe, but further overstretching or over-exertion is ill-advised and dangerous in the prolongation of symptoms or development of complications. Light massage, active and passive movements of the muscles involved, should be the practice regardless of the age of the subject. It is not necessary to use anything by way of a lotion or liniment to lubricate or counter-irritate during massage or subsequently for dressings. The unmedicated surface may be very properly massaged and manipulated by a proficient masseur, without these. This fact is stressed because it is believed that aside from the psychic effect little value is found from the use of solutions or other preparations during a masseur's regular procedure.

Sprains (*Cont.*)

which allows for observation of the part, without movement, is advised. The ice-bag with mild pressure may be applied in these severe cases. If heat is preferred for the comfort of the patient, it is to be applied in the dry form. After a subsidence of the symptoms, and more especially after the reduction of the swelling, the plaster cast should be applied. The part should, generally considering all parts, remain immobilized for at least 50 per cent of the time allowed for immobilization of a fracture. For periods, even up to twenty-one days, the cast may be of the continuous variety. Where a longer time for immobilization is required, the cast should be of the split or bivalved variety. It is valuable to encourage use of every part of the body not incorporated in the cast. When the shell is removed we come to the consideration of convalescence.

Convalescence of Sprains: is speedy after the removal of the immobilization dressings. From this time the treatment of sprain simulates that of strain. Gradual functioning of part to full efficiency is, however, more guarded and slow. Frequently there is more confidence in the use of the part involved with the wearing of an elastic stocking or light leather cover over the area for a short time. This snug fitting support affords a feeling of security, but it must be worn only during the times for functioning and not for any indefinite or long period.

Conclusion: This subject is not treated with anything resembling the fullness which it merits, but it is hoped that a program for liberal expression upon the consideration of the strains and sprains discussion is herewith introduced.

POSTOPERATIVE MANAGEMENT OF APPENDICEAL PERITONITIS*

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THE treatment of appendiceal peritonitis may be divided into 3 stages, namely, before, during and after operation. The period before operation is important, not so much from the standpoint of what is done as of what is not done. It is in this period that the decision when not to operate depends upon mature judgment and the courage born of long experience. It would be impossible to set down guiding principles to apply in every case of peritonitis. The course of action must be determined in the mind of the surgeon who sees the patient and it will be determined by his interpretation of the patient's symptoms, the evaluation of physical findings and particularly upon whether the peritoneal infection is diffused or localized. Briefly, the types of peritonitis are the localized, spreading, and the diffused. It is important to bear in mind that this classification does not depend upon the size of the area of peritoneum involved but on the nature and activity of the process which is going on within the peritoneal cavity. The term "general peritonitis," usually is used incorrectly. It is very uncommon to find the entire peritoneal cavity infected since the patient usually succumbs before this condition is reached. Localized peritonitis may occur early in appendicitis when the infectious process has been isolated and confined by a protective barrier made up of neighboring coils of bowel, omentum and peritoneum. It may occur in the subsiding stage of diffused peritonitis when the resisting and protective forces of the peritoneum have stayed the progress of the spread of the infection and caused it to remain confined to a limited area. In spreading peritonitis there are no protective barriers and the infectious process is being actively disseminated without apparent resistance on the part of the peritoneum. This condition if unchecked becomes diffused peritonitis. Peristaltic activity becomes quiescent, distention appears and the condition of the patient is that of severe toxemia. There is abundant absorption of toxins by the peritoneum and the final issue waits as the balance between the forces of infection and the protective properties of the peritoneum and the general resistance of the patient decide the victory for good or evil. To open the peritoneum during this stage or to disturb in any way the patient's battling forces of resistance is to tip the balance in favor of infection and death. General supportive measures, abundance of fluid and anatomical rest best serve the patient. In a few hours it will be decided whether the patient can weather the storm. If successful, the invading forces will be checked then pushed back and confined to a large or small area on the right side of the abdomen. Peritoneal activity will be resumed. Tenderness and rigidity will be localized. The pulse will become less rapid but the temperature will remain high. This is the opportune time for surgical intervention. The surgical condition is essentially that of a large suppurative collection. The indicated procedure is removal of the source of infection, namely, the appendix, and thorough drainage of the abscess cavity. Spinal anesthesia is of distinct advantage because it permits a deliberate attack without undue haste. During the operation two factors make for success, namely, protection of the uninvolved peritoneum by the proper disposition of gauze, and thorough drainage provided by gauze and rubber tubes and a wide open wound. Following a properly

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conducted operation the subsequent treatment must be conducted along lines which recognize that peritonitis is still present and that the activity of the infection has been exaggerated to some degree by the mechanical intervention.

The sound principles of the Fowler position are very often defeated by careless practice. The proper maintenance of this position requires almost constant attention on the part of the nursing staff, otherwise, the patient slips into the hollow of the bed and assumes a drooping and cramped attitude. Under these circumstances there is, not only failure to maintain dependent drainage of the peritoneum but the structural deformity seems to favor abdominal distention, vomiting and dilatation of the stomach. We have secured more satisfactory results by elevating the head of the bed to an angle of about 20° by placing blocks under the bed posts. In this position the patient does not slide down in bed, the spine is not flexed and he is more comfortable.

The use of morphine is confined entirely to the control of pain and restlessness. Usually one or two doses are sufficient. Atropine is not used because we believe that it favors distention by its paralytic action on the intestinal musculature. It also contributes to excessive thirst.

The administration of an abundance of fluid is the most important single therapeutic item. Fluid is not given by mouth because it is usually retained in the stomach until vomiting occurs. Large quantities may be given by proctoclysis but this method has the disadvantage of causing distention of the bowel particularly of the proximal portion of the colon, a region which should not be disturbed. For the administration of fluid we have come to rely principally on hypodermoclysis and intravenous infusion. Two thousand cubic centimeters of fluid can be given under the skin during twenty-four hours and with proper technique and management the dosage is not disturbing to the patient. When so given it is sure to reach the circulation and it maintains a reservoir of supply for constant use. Intravenous infusion is used when other avenues are insufficient or when the acute crisis of toxemia demands an immediate supply of fluid to the circulation. Glucose in 50 per cent solution is given intravenously as a supportive measure.

Abdominal distention is usually caused by accumulation of gas in the stomach and in the large bowel. The latter condition at times may be relieved by insertion of a rectal tube. The passage of the stomach tube is disturbing to the patient and to the quiet of his abdomen. A Jutte tube introduced through the nose may be readily passed into the stomach without disturbing the patient. It serves to empty the stomach of fluid and gas. While it is in position the patient may be given water by mouth to satisfy his thirst and there will be no danger of accumulation in the stomach. It is not uncommon to have the patient become quiet, comfortable and even to fall asleep after the introduction of the Jutte tube. Vomiting is promptly relieved.

Happily the days are gone when brisk purging was prescribed during the first two or three days after operation for the purpose of reducing abdominal distension. The principles of physiology are ignored by the old textbook term, paralytic ileus. Only a dead gut can be spoken of as paralyzed. The general musculature of the entire alimentary tract is under the control of the parasympathetic nervous system. It will be recalled that in this scheme of innervation there are terminal ganglia in the walls of the gut which are capable of independent action when the preganglionic fiber has been destroyed. In general it may be stated that the parasympathetic nerves of the alimentary tract are essentially motor and that they react to stimulation by causing muscular contractions. There is also an important innervation by sympathetic fibers. These come from the thoracico-lumbar outflow of the spinal cord and terminate in large extrinsic ganglia which are located at a distance

from the structure in which the postganglionic fiber finds its agent. The sympathetic has an inhibitory action on the general intestinal musculature, that is, it acts to decrease tonicity. Along the intestinal tract are certain sphincter muscles or sphincteric mechanisms, to wit, the pyloric sphincter, the sphincter of Oddi, probably one at the duodenojejunal juncture, the ileocecal sphincter, probably one at the cecocolic juncture, and the rectosigmoidal sphincter.

There is evidence to indicate that the sympathetic supplies the motor fibers to these sphincters (Gaskel). Under normal conditions there is harmonious coordination between parasympathetic and sympathetic influence which makes possible peristaltic activity and the onward progress of intestinal contents. It appears that the toxemia of peritonitis gives rise to an overactivity of the sympathetic nervous system as evidenced by the blanched, cold and leaky skin and by a general bodily behavior which for want of a better term has been called surgical shock. Within the abdomen, the evidence of hyperactivity of the sympathetic system is intestinal distension. If the assumption is correct that stimulation of the sympathetic fibers causes relaxation of the gut and contraction of the sphincters then distension is explained. Further proof that distension is not a state of paralysis is the fact that following the administration of a spinal anesthetic it promptly disappears. In an extended use of spinal anesthesia I have noted frequently that when the abdomen is opened there is exaggerated peristaltic activity and irritability. Spinal anesthesia truly paralyzes the sympathetic fibers which have their origin in that part of the spinal cord reached by the anesthetic agent. The nerves of the general musculature of the gut are not paralyzed because their origin is high in the cord (vagus) and out of reach of the anesthetic. From the standpoint of pathologic physiology, what is to be done for the relief of abdominal distension? Inquiry has revealed that it affects principally the stomach and colon probably by reason of incoordination or spasm of the pyloric and rectosigmoidal sphincters. (More pronounced manifestations of the incoordination of these sphincters are infantile pyloric stenosis and Hirschsprung's disease.) The stomach can be emptied and kept so by the use of the Jutte tube. Colonic distension is more difficult to relieve. If extreme, a spinal anesthetic will give prompt results and thus obviate the necessity of making a cecostomy. In milder cases, the use of proctoclysis probably aggravates the condition. It is better to give fluid by hypodermoclysis. A rectal tube passed beyond the rectosigmoidal sphincter with the aid of a proctoscope should relieve the gas distended colon, but this method under the trying conditions presented by a very ill patient is not practicable. Magnesium sulphate has a local sedative action on spastic smooth muscle. It has been successfully used as a local application to the region of the rectosigmoidal sphincter in the treatment of chronic constipation. For several years I have discarded the use of the routine enemas after operation because they are too voluminous, too fatiguing to an ill patient (pulmonary embolism has been reported in causal relationship), and because they are usually ineffectual when most urgently required. Experience has demonstrated that colonic distension is usually overcome by the rectal administration of a small quantity of magnesium sulphate solution. Six ounces of a saturated solution are injected into the rectum with a catheter or syringe and permitted to remain. In half an hour, sometimes longer, the patient has a desire to defecate and will pass quantities of flatus and fecal matter. And there will not be the feeling of depression and weakness which so frequently follow the ordeal of the usual enema. This enema may be given on successive days until distension is permanently relieved. Theoretically, the magnesium sulphate by direct contact relaxes the spastic sphinteric mechanism

of the rectosigmoid. In practice too it works. The fatal agent of peritonitis is overwhelming toxemia made possible by the extensive absorptive area of the peritoneum which exceeds the skin surface of the body. The speed of absorption, other things being equal, is the determining factor in recovery or death. Certain bacteria as the colon bacillus cause an inflammatory reaction in the peritoneum giving rise to an outpouring of lymph and plastic exudate. These are protective forces and delay absorption. Antecedent peritoneal trauma as from operation, in clinical experience, seems to increase peritoneal resistance. Other bacteria, as the streptococci, encounter little resistance from the peritoneum or speedily overcome it, disseminate rapidly, have their toxins freely absorbed into the circulation with the usually fatal issue. Handley holds that intestinal obstruction (ileus duplex) is the cause of death in practically every case of fatal peritonitis. With this, surgical opinion is not in accord. There is no doubt that at times intestinal obstruction supervenes after operation for appendiceal peritonitis. Its most frequent site is the terminal ileum which may be thickened almost to occlusion by extension of inflammation from the abscess cavity of which it partly forms the wall. It is the admonition of Deaver that this potential danger should be recognized at the time of operation and, when present, an ileocolostomy should be done as part of the primary operation.

The general appearance and behavior of the patient suffering from the toxemia of peritonitis suggest a condition of intense stimulation. Cerebration is acute, the pulse is rapid and of small volume and the temperature is high prior to the terminal stage. In a clinical sense the condition is not much unlike a hyperthyroid crisis. Others have noted a suggestive thyroid overactivity in acute infections. Iodine has a specific influence in controlling hyperthyroidism. With this thought in mind, during the past year I have given Lugol's solution, 1 dr. to the pint of water by protoclysis, to patients having peritonitis. To date my experience has been too limited to warrant conclusive statements. Decidedly beneficial results have been noted, but other factors must be considered which make any inference regarding the effect of iodine a hasty deduction.

The prime reason for use of drainage is maintainance of free communication between abscess cavity and the exterior. A large area of the peritoneal cavity like that in diffuse peritonitis obviously would be impossible to drain. The operative essentials of management of localized peritonitis are adequate incision without thought of incisional hernia, wide open drainage to the utmost limits of the infected area and meticulous care to avoid breaking protective barriers into uncontaminated regions. The use of certain drains is a matter of personal choice. The main objective is an open wound whose free exit from the abscess cavity must not be obstructed by sutures or partially obliterated by the efforts of intra-abdominal pressure. When should the drainage material be removed? Often too early; never too late. It is usually wise to let it come out of its own accord. The exit of pus may be obstructed by improperly placed drains but not by a drain which goes to the bottom of the infected cavity. When the drain is out, the wound should be kept open to its depths and permitted to heal by a gradual filling-in process. Irrigation of the wound is a questionable practice. It may be harmful. No evil can come from pus which is not under tension. Efforts to sterilize the wound, to be followed by secondary closure, are attended by many failures and doubtful advantage when successful. Postoperative intestinal obstruction during convalescence is a difficult diagnostic problem. The symptoms which persist for a few days after operation for appendiceal peritonitis, the postoperative ileus and distention and vomiting so closely simulate obstruction as to make differentiation uncertain. Yet the diagnostic urgency makes delay seem

extremely hazardous. However, when this question arises during the first four or five days after operation a waiting policy is safer. Many of these cases in which obstruction seems to be present will subside spontaneously. To reopen the abdomen in the presence of peritonitis is attended by great risk. It becomes a matter of choosing the lesser of two evils: that is, masterful inactivity. It is the practice of some surgeons to make an enterostomy in these cases of questionable obstruction hoping thereby to err on the side of safety. Adequate statistics on this procedure are not available. It is difficult to conceive how a jejunostomy, draining only a short segment of bowel, could be beneficial in the type of intestinal obstruction here considered. There is much to indicate that it is often actually harmful. It does not release the obstruction. It forms a jejunal fistula which in experimental work has proved to be more rapidly fatal than high intestinal obstruction. The solution of the problem seems to be first, recognition of potential obstruction at the primary operation and prevention by a short circuit anastomosis (ileocolostomy) as advocated by Deaver, and second, if this has not been done and symptoms of obstruction arise which cannot be differentiated from peritonitis, follow a policy of watchful waiting. Murphy said, "There is no more perplexing problem in all surgery than to decide when to reopen the abdomen with symptoms of postoperative ileus; the more experience one has the more one appreciates the inadequacy of diagnostic guides."

SPINAL ANESTHESIA USED AS A PREOPERATIVE INDEX TO GANGLIONECTOMY IN MEGACOLON*

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IN 1927, Wade and Royle reported: In a series of 25 cases of congenital spastic paraplegia in which bilateral lumbar sympathetic ramisection was performed, 13 patients suffered from chronic constipation, and 11 were relieved. In a number of these cases a dilated colon was found at operation.

Wade later reported 4 more cases in which ganglionectomy was done with unsatisfactory results in two. Ganglionectomy for megacolon is now being used with increasing frequency and a proper index for the selection of such cases for this operation is highly desirable.

In brief, our method has been to give a patient what may be called a spinal anesthesia test. The patient is given a barium enema and an *x*-ray taken of the entire colon. This is the control picture. Then a high spinal anesthesia is performed and a series of radiographs taken. If the colon becomes active and shows peristalsis and a decrease in size, the case is considered as a satisfactory one for ganglionectomy.

RATIONALE

The interpretation of this test deals entirely with the nerve supply of the large gut. The myenteric plexuses of Auerbach and Meissner have the sole action of producing contraction above and relaxation below the point stimulated. The sympathetic nerves arise from the fifth dorsal to the sacral segments of the cord, are distributed mainly through the four lumbar ganglia, and when stimulated produce dilatation of the colon. The parasympathetic system consists of the cranial branches through the vagus controlling the ascending and proximal half of the colon, and the sacral branches supplying the remainder of the large gut.

The object of the test is to produce a blocking of the thoracicolumbar outflow of the autonomic nervous system by spinal anesthesia. This also blocks the sacral parasympathetics as well as the entire cord as high as the level of analgesia leaving only the cranial parasympathetics to exert their full influence. The portion of the gut to be observed then, is the ascending and transverse colons.

The test then is, in part, a temporary ganglionectomy. What remains to be studied is whether this test conforms with postoperative findings, and if so, to what extent. The test has been used by us on 1 case with completely successful results. It also answers the unsuccessful results of operation in certain cases n that they were not due to a hyperactivity of the sympathetic system.

CASE REPORT

The patient, admitted July 8, 1930, to St. Mary's Hospital, is a young woman of twenty-three years of age, who ever since she could remember had marked constipation and irregular periods of distension particularly after carbohydrate ingestion and headaches for which she used many aspirin tablets. The most distressing symptom, however, was the presence of severe crampy epigastric pains radiating to the left and to the back. Elsewhere an appendectomy was performed on her two years ago, and following this all her symptoms became aggravated. The constipation became absolute; laxatives and purgatives produced no effect; she actually bought gallons of mineral oil but only an enema gave some relief. The attacks of pain increased in frequency and severity. The headaches became worse; periods of distension still recurred though she remained on a carbohydrate-low diet for months.

Physical examination revealed a fairly well developed young woman with all systems negative for abnormalities except for tenderness

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under the left costal border and costovertebral angle. Examination of the urine showed it to be alkaline of specific gravity 1019, and negative for albumin and sugar. The blood showed 80 per cent hemoglobin; 4,600,000 erythrocytes; color index of 0.8. The white cells numbered 8100 with 62 per cent neutrophils, 32 per cent small lymphocytes, and 6 per cent endothelial leucocytes. Kahn test was negative. Temperature ranged from 97 to 99°F.; pulse from 60 to 80.

She was first referred to the Medical Service where a cystoscopy and pyelogram were done with negative findings. Rectal examination revealed a posterior fissure and sentinel pile, and a hemorrhoidectomy was performed. Since there was no amelioration of the symptoms she was considered a neurotic. A barium enema was given and she was found to have a massive dilatation of the entire colon, especially the proximal half with a low-hanging transverse colon. She was then referred to the Surgical Division and the test was first tried on her as follows:

1.00 P.M. Barium enema and *x*-ray. Control (Fig. 1).

1.10 P.M. Spinal anesthesia with 200 mg. novocaine crystals.

1.20 P.M. First test ray. Anesthesia at level of epigastrium.

1.40 P.M. Second test ray. Anesthesia at level of clavicle, i.e., fourth cervical (Fig. 2).

2.15 P.M. Third test ray. Same height of anesthesia.

3.15 P.M. All anesthesia gone.

Next day at 10.00 A.M. Fourth test ray.

Preoperative preparation included a low carbohydrate diet; daily soapsuds enema; ½ oz. mineral oil three times daily after meals; and $\frac{1}{30}$ grain strychnine sulphate by mouth twice daily.

Operation was done on August 22, 1930, under ether anesthesia and lasted one and one-half hours. Adson's intraperitoneal approach was used; on the right side four lumbar ganglia were removed and on the left only three for the first ganglion was abnormally high. The colon was found markedly distended; no adhesions at all were present as a result of the previous appendectomy.

The postoperative course was not uneventful in the first week. The patient had two sudden attacks of dyspnea, palpitation and numbness followed by anesthesia over the right half of the body; both attacks lasted one hour and were entirely relieved by morphia.

This was followed for several days by sharp shooting pains in her legs. After three weeks the patient was allowed to get up. It is now eight months after the operation and the results are as follows:

a. Gain of 20 lb. in weight.

b. General feeling of well-being.

c. *Regular* daily bowel movement since operation (sometimes two in one day) *without* the use of laxatives.

d. Fluoroscope shows twenty hour elimination (Fig. 3).

e. Barium enema and *x*-ray of colon show result to be even better than that shown by test. Fluoroscopy shows a live active colon.

f. Entire cessation of headaches.

g. No attacks of abdominal pain.

COMPARISON OF TEST WITH RESULTS OF OPERATION

Even in the large dilated colon, under fluoroscope, there were varying periods of inactivity and slight activity. This activity became much greater during the test and following operation. To accurately compare results on several fixed films is a very difficult matter for it does not denote the constant change of size, shape and amount of peristalsis. Even with this in mind, a comparison of the films in this case is justifiable and represents the actual state.

The following are the widths of the colon during the test and after operation:

	Control	1st ray	2nd ray	3rd ray	Postoperative
Ascending	4	3	3	3	2
Proximal ½	4	3	3	2	2½
Distal ½	3	2½	2½	2	2½
Descending	2½	2	2	2	2

During the test peristalsis increased in depth and frequency and the transverse colon became elevated. The findings of this test conform well with the parasympathetic innervation of the large gut; the cranial portion supplying ascending and proximal two-thirds of the transverse colons, and the sacral portion the remainder. And it is over the area supplied by the vagus that shows the greatest changes.

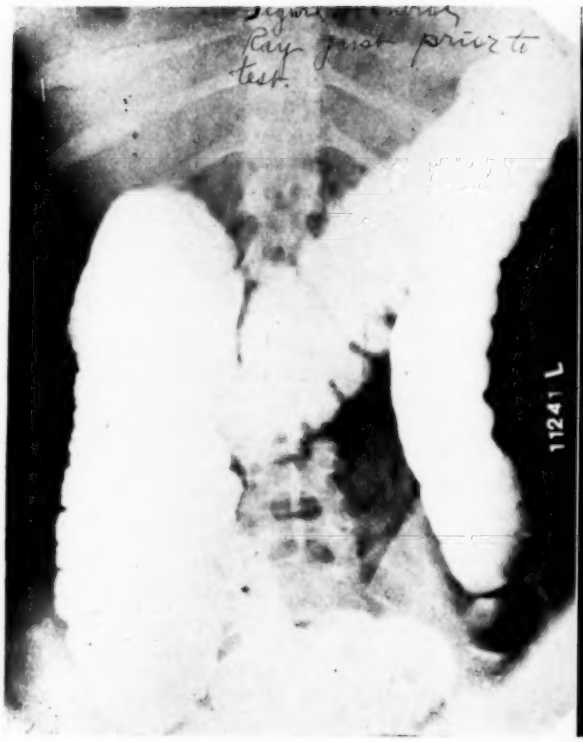

FIG. 1. Control ray just prior to test.

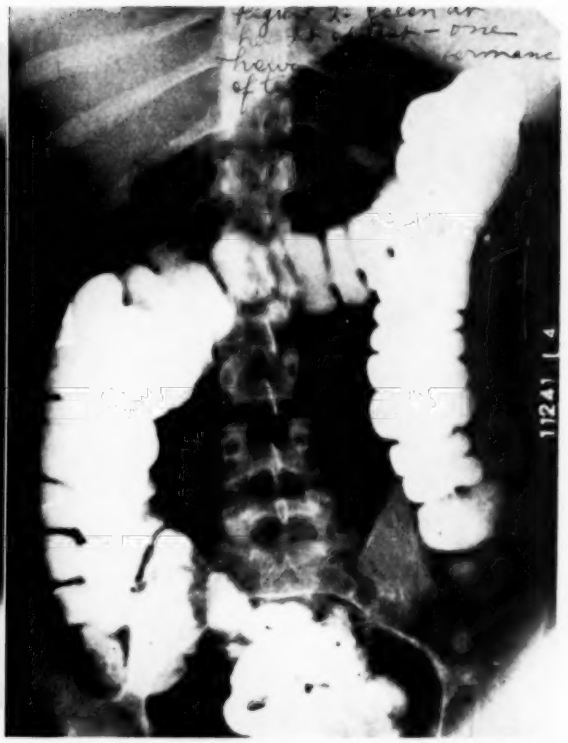

FIG. 2. Colon at height of test one hour after performance of test.

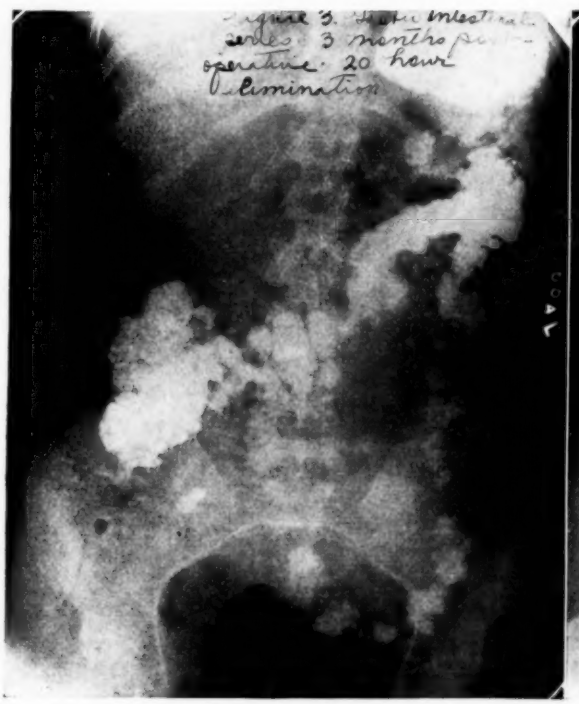

FIG. 3. Gastrointestinal series three months postoperative. Twenty-hour elimination.

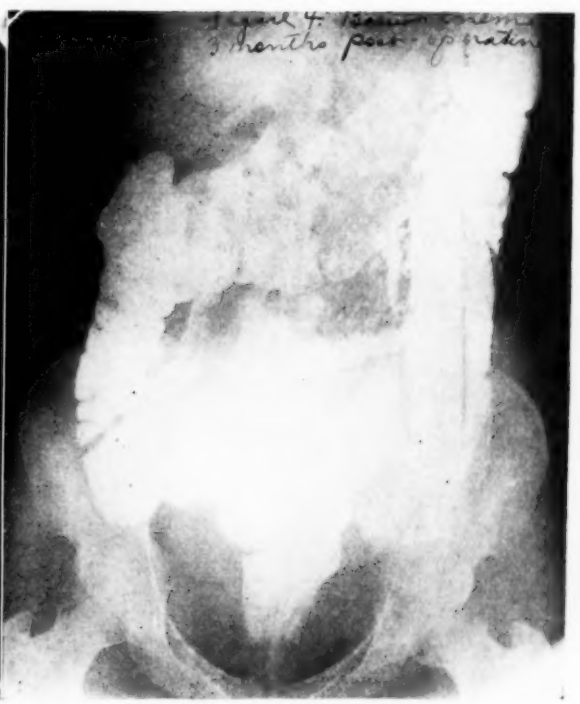

FIG. 4. Barium enema three months postoperative.

One may conclude then, an existing hyperactivity of the sympathetics. In the distal half of the gut where both sympathetics and

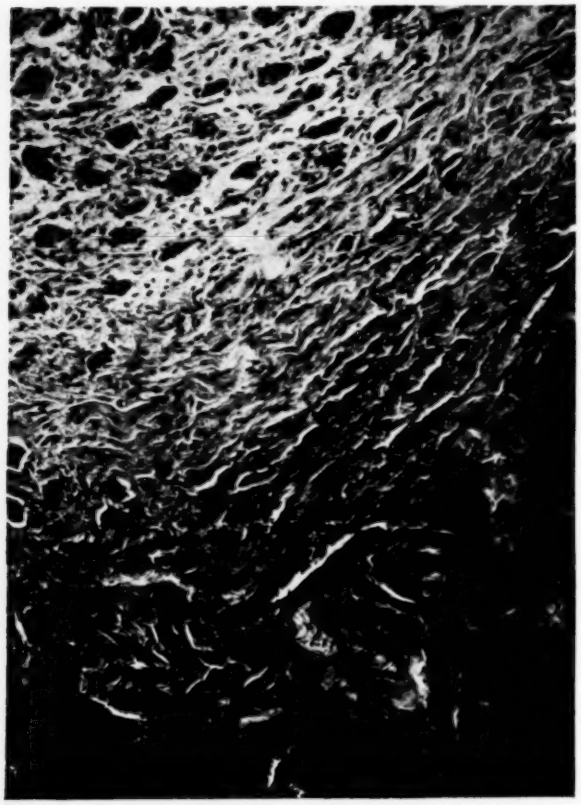

FIG. 5. Note wavy fibrils irregular sized nuclei and diminished size of stromal nuclei.

parasympathetics are blocked one would expect to get no changes, but there is increase peristalsis with practically no change in the width of the gut. Postoperative results are even better than those found during the height of the test, due probably to the greater time given for readjustment of the parasympathetics. Thus, postoperative results compare favorably and are even slightly better than those during the test. The test, then, is not only an index to operability but also gauges roughly the amount of benefit to be expected.

PATHOLOGY

The pathological report was prepared by Dr. James E. Davis and is as follows:

Microscopic Examination: Section is a sympathetic ganglion exhibiting some irregular thickening and irregular hyalinization of the blood vessel walls and narrowing of the lumina. There is slight hyalinization of the stroma and some contraction of the entire tissue with slight atrophy of some of the nerve cells. There is some increase in cellularity, doubtless due to contraction.

Section is of lymph node tissue and fatty structures and shows Grade 2 of vascular sclerosis and hyperplasia.

Diagnosis: Mildly sclerotic ganglionic tissue.

The pathological inference is that of a toxic factor being the cause for the clinically hyperactive ganglia and the degenerative changes shown in them.

DISCUSSION

The advantages of the test are threefold: it offers a method of selection of cases for ganglionectomy; it eliminates needless operations; and it gives a rough measure of the benefit to be desired.

From the etiological point of view, it divides megacolon into two large types, those due to a sympathetic hyperactivity and those due to other causes.

It is the former type of case which is benefited by ganglionectomy; and this test selects that case. The same test may be used in the atonic types of severe constipation which may be considered for this surgical procedure. A further use of this test lies in cases of Raynaud's, Buerger's and other vaso-obstructive conditions where calorimetric measure of the blood flow of the limb both before and during the spinal anesthesia may be determined and the increase in blood flow determined. If there is a great increase in blood flow, the case then is suitable for ganglionectomy.

CONCLUSIONS

1. The spinal anesthesia test may be used as an index to ganglionectomy for megacolon.
2. A case of megacolon is described on which both test and operation were done with complete confirmation of results.
3. Etiologically, megacolon may be divided into those cases due to sympathetic hyperactivity and those due to other causes.
4. The test may be further used in the vaso-obstructive conditions considered for ganglionectomy.
5. Pathological lumbar ganglia are reported.

SPINAL CORD COMPRESSION:

TUMORS AND ALLIED NON-TRAUMATIC CONDITIONS*

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TUMORS of the spinal cord rank first among those neoplasms, which if diagnosed and removed early in their development, can be permanently cured. The symptoms produced by these lesions result from compression of the spinal cord within its bony compartment. Consequently, any condition producing compression of the spinal cord may simulate tumor so closely that a differential diagnosis is very difficult.

Trauma, infection and neoplasia, associated with compression, usually can be accredited with derangement of function of the spinal cord. A history of injury, together with roentgenologic evidence, is generally sufficient for a diagnosis of traumatic myelitis; furthermore, the history and cytologic examination of cerebrospinal fluid commonly give sufficient evidence for a diagnosis of acute infectious myelitis. But slowly increasing pressure on the spinal nerve roots, and on the cord itself, by chronic infective and neoplastic processes, including tumors, creates such a multiplicity of symptoms that in some cases a differential diagnosis is impossible until laminectomy is performed.

However, a differential diagnosis between compression of the spinal cord and degenerative lesions of the spinal cord should be made by means of a complete neurologic examination, including tests which will elicit any changes in the motor or sensory functions of the cord. The physician should carefully examine the change in reflexes and vibratory responses, as well as in the spinal fluid, with particular attention to change in pressure, color and cytology. Lipiodol should be used in conjunction with a complete neurologic examination in order further to establish diagnosis. A roentgenogram of the vertebral column, as well as examination for primary malignant disease, is also significant.

Surgical Intervention: Exploration of the spinal cord and its membranes carries with it little risk and can be done with minimal loss of function. In many borderline cases, preoperative pathologic diagnosis is almost impossible, and in spite of clinical syndromes and neurologic observations, the diagnosis is made at operation.

The consensus of opinion among neurosurgeons seems to be that in any case of dysfunction of the spinal cord, due to slowly developing compression, exploration should be carried out, provided that a distinct level of sensory disturbance is present and definite subarachnoid block can be demonstrated. No two patients give the same history or present the same evidence on neurologic examination. Certain clinical developments, such as the cycle described by Frazier; namely, root pain, Brown-Séquard syndrome, and paralysis, may be evident but this classical progression of symptoms is seldom seen. Loss of sphincteric control due to compression of the spinal cord usually comes late in extramedullary tumors and early in intramedullary involvement; frequently, however, sphincteric function is lost early in an extramedullary lesion.

Cases also are observed in which the history is classical for tumor, but when exploration is made, the pathologic changes of the spinal cord prove to be inflammatory rather than neoplastic. Again, the most bizarre of histories and signs may be produced by a simple neurofibroma or endothelioma. Consequently, the pathologic changes in compression of the spinal cord should be of primary consideration in any surgical discussion.

Laminectomy can be performed by

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several different methods. Mechanical removal of the spine and laminae is not so important as close observation of the tissue removed. The texture of the removed bone should be carefully scrutinized for evidence of any changes, either of absorption or of overgrowth. Then the epidural space requires a critical survey for signs of neoplastic or inflammatory changes. If the exploration has been negative up to this point, then the dura should be carefully examined for any abnormalities of pulsation. Absence of pulsation means one of two conditions: either the compression is above the laminectomy opening or the exposed dura lies just over it. Gentle palpation of the dura rules out the latter condition, and if there are no signs of compression, the laminectomy must be carried cephalad until there is definite pulsation of the dura. During the operation, it must be kept in mind that accurate as the localization has been, there is always danger that the level of the abnormality, as determined before operation, may be one segment lower than the actual compression of the cord.

After it has been demonstrated that the cause of compression is not extradural, and the pulsating dura has been exposed, operation should proceed by incising the dura longitudinally. Should no cause of compression be evident, and the operator be at a loss to explain the absence of pathologic change, then a silver probe or soft rubber catheter should be gently inserted intradurally to eliminate the possibility of an obstruction either above or below. The cause of the compression may lie anteriorly to the spinal cord and perhaps can be exposed only after the cord has been rotated by means of the dentate ligament.

Lesions within the spinal cord may cause compression. The majority of these lesions involves a discouraging prognosis; yet cysts have been evacuated, benign tumors have been completely removed, and recovery has resulted from the decompression incidental to the laminectomy.

Complicating the preoperative pathologic diagnosis of tumors of the spinal cord are inflammatory lesions which develop insidiously, and which simulate such tumors so definitely that a differential diagnosis can be made only at operation. Pachymeningitis due to tuberculosis, syphilis, or other chronic inflammatory lesions may prove to be the cause of compression. Chronic cystic arachnoiditis may be encountered when the dura is opened. Varicosities of the meningeal vessels may simulate tumors, although such a condition may be found adjacent to tumors, making the diagnosis of varicosity possible only after the presence of a tumor has definitely been excluded. The surgical and pathologic aspects of compression of the spinal cord are so closely interwoven that until a complete examination of the vertebrae, meninges and cord has been carried out, the operation should not be terminated nor the diagnosis completed.

Pathologic Changes: A review of the literature of the tumors of the spinal cord reveals that the pathologic classification is more or less in a state of chaos. This may be explained by the great diversity of opinion between pathologists, and is readily understood when the different fundamental principles are considered. The three primitive germ layers, namely, endoderm, mesoderm and ectoderm, were selected as the progenitors of all tissue structure, and it was believed that any tumor must develop from one of these layers. Following closely on this came the "cell rest theory," which assumed that inclusion of embryonic tissue took place during development, and that the included tissue lay dormant for an indefinite period, and then suddenly became active. Proliferation of these cells resulted in tumors and rapidity of growth, and the presence of a restraining capsule determined whether they were benign or malignant.

As time advanced, the search for the causative factor of tumors was directed to the predominating cell. Taking into consideration the different stages of the development of the individual cell, it was

discovered that there were reserve cells for every type of cellular structure. These embryonic cells had the potentialities for developing into certain specialized adult cells, but under the influence of an environmental change, they might alter their function. It was also discovered that these embryonic reserve cells, regardless of their supposed parentage, closely resembled one another. Then a cytologic resemblance between malignant tumor cells and embryonic tissue cells was emphasized. From this developed a biologic conception of neoplasia, which placed a pathologic classification on a logical basis. According to this conception, metaplasia, when reviewed from a cytologic standpoint, offers an explanation for extraordinary and unusual cellular structure. Likewise, malignant tumors are comprehended with greater facility because they appear to be due to hyperplasia or to multiplication of reserve or embryonic cells. Finally, the grading of malignant tumors was made possible by the evaluation of the amount of cellular differentiation found on microscopic examination.

From the brief outline of the different premises on which pathologic analysis has been based, one can readily understand the difference of opinion, even among leading authorities. To complicate further the nomenclature, as applied to neoplasms, the surgical pathologists who deal with fresh tissue, and the surgeons who base their conclusions on clinical, surgical and pathologic evidence, have added observations to the literature.

For this reason, an attempt has been made, by means of an orderly, systematic analysis of tumors of the spinal cord encountered at the operating table, to develop a more intimate interrelationship between the diagnostic, surgical and pathologic aspects of such tumors. The following pathologic analysis is based on accepted and authenticated terminology, and microscopic studies have been carried out by means of fixed frozen sections stained with hematoxylin and counterstained with eosin. These observations are to be used as a basis for further study with various special stains which probably will eliminate many points about which there now seems to be a diversity of opinion.

The following tabulation, based on a series of 312 cases, illustrates the multiplicity of tissue changes which can cause compression of the spinal cord.

The tabulation, although useful as a comprehensive summary of pathologic observations, might prove confusing; so, for the sake of convenience, a simpler grouping, intradural, extradural and intramedullary, has been used. The relative frequency and the anatomic distribution of the lesions in 312 cases were as follows: extradural, 67 cases; intradural, 156 cases, and intramedullary, 89 cases. What is to follow is based largely on a consideration of these 312 cases.

EXTRADURAL TUMORS

Any condition of compression of the spinal cord which clinically could not be distinguished from actual neoplasm has been included in this series. Metastatic lesions, tumors of the bone and intervertebral disks, as well as inflammatory lesions, may be found at operation and may or may not have been diagnosed before operation.

Knowledge of the tumors which the surgeon may encounter is always to be desired. Meyerding has classified tumors of the bone, using the bones of the extremities as a basis. But the same tumors may occur in the vertebrae and cause compression of the spinal cord. Rand recently reported cases of extradural coccidioidal granuloma which seem to occur only in the southwestern part of the United States or Mexico. Echinococcus or hydatid cysts have been reported as causing compression of the spinal cord; they also are thought to be confined to certain regions of the body but they may be encountered when least expected. The extradural lesions have been grouped and listed according to their pathologic diagnosis and frequency of occurrence as found at operation.

Fibroma (3 *Cases*): The first tumor of the spinal cord removed by Horsley was an extradural fibroma. These fibroblastic tumors are not common, and yet they are sufficiently common to be significant because of their benign character. Fibromas may arise from any fibroblastic structures of the spinal cord and may be intramedullary, intradural or extradural. The tumors referred to in this paragraph were simple fibromas; the neurofibromas and the fibrosarcomas were not included.

Lipoma (1 *Case*): According to Frazier, lipomas are rare except when associated with spina bifida and they usually are found in the lumbar region. The one extradural lipoma was removed from the cervicodorsal region. These fatty tumors develop slowly, on gross examination somewhat resemble fibromas, and in spite of their softness may inflict serious pressure on the cord.

Glioma (2 *Cases*): Extradural gliomas are probably extensions into the epidural space of tumors of the spinal cord, or according to Kernohan, they may be heterotopic masses of glial cells growing in the meshes of the pia arachnoid. Diagnosis was made from tissue removed during laminectomy for an extradural tumor. An apparently malignant tumor was encountered following removal of the spines and lamina. It was so extensive that further operation was contraindicated.

Osteoma (3 *Cases*), *Osteosarcoma* (2 *Cases*), *and Hypertrophic Osteitis* (7 *Cases*): Boyd, in a consideration of the osteogenic group of neoplasms, pointed out the difficulty in determining whether any new formation of bone should or should not be regarded as a true neoplasm. There are many inflammatory and traumatic conditions associated with formation of bone, such as the callus of fracture, the ossification of inflammatory exudates in various parts of the body, and the bony outgrowth around joints, which are the seat of chronic arthritis. These do not present any essential differences from the masses of bone which are recognized as true osteomas. The microscopic picture is of little value as a means of differentiation except in the case of malignant change. The condition described as hypertrophic osteitis, or hypertrophic osteoarthritis by Parker and Adson, is really an overgrowth of soft, spongy, vascular bone, inflammatory in character, which constricts the vertebral canal and may be associated with an overgrowth of bone around the vertebral foramina. A preoperative diagnosis of this condition is rather difficult, due to the fact that roentgenologic examination is not of marked value.

Metastatic Tumors: Carcinoma (1 *Case*), *Fibromyxosarcoma* (2 *Cases*), *Fibrosarcoma* (1 *Case*) *and Hypernephroma* (1 *Case*): Woltman had aptly stated that metastasis of malignant tumors to the central nervous system is a derelict encountered in our diagnostic lanes. Unsuspected primary lesions may be responsible, and therefore metastatic lesions must be eliminated from consideration by careful general and neurologic examinations. Fortunately, the nature of the lesion generally can be detected by roentgenograms, and Woltman has studied 136 cases in which the condition was diagnosed by roentgenologic methods in 98. The symptoms may be the same as those of any benign tumor of the cord except that the progress of malignant growth is usually more rapid. Often when no primary growth can be found and sometimes when primary malignancy is evident, as in the 2 cases of fibromyxosarcoma of the uterus and in the case of fibrosarcoma of the popliteal space, exploration should be done, not only to establish a diagnosis but also as a palliative measure.

Whenever a patient presents the picture of rapidly developing compression of the spinal cord, with all of the clinical manifestations of a tumor of the spinal cord, and without evidence of primary malignancy, exploratory laminectomy should be done as a diagnostic as well as a palliative measure. Such was the situation found in 1 case of metastatic hypernephroma. At operation, a malignant tumor was found compressing the cord in the epidural space. On gross

examination the tumor presented the characteristic yellowish-red, granular, friable appearance, and on microscopic examination, the usual malignant cells, distended with gelatinous material, the so-called foamy cells of hypernephroma, were found. The etiology of hypernephroma has long been a subject of dispute. Ewing expressed the belief that this type of tumor is a papillary carcinoma primarily of nephritic origin, whereas Grawitz formulated the conception that certain tumors of the kidney were derived from suprarenal rests. Malignant tumors of the type of hypernephroma are always prone to metastasize to bone. Sometimes the most exhaustive search for a primary focus may prove unsuccessful, and only during exploratory laminectomy is metastasis to the spine encountered.

Sarcoma (2 Cases) and Lymphosarcoma (2 Cases): Clinically the diagnosis was extradural tumors of the spinal cord, and at operation a cellular tumor was encountered which filled the epidural space. As much of these tumors as possible was removed, and on microscopic examination 2 of them were found to be sarcoma and 2, lymphosarcoma.

Neurofibroma (13 Cases): This tumor, designated by Penfield as perineural fibroblastoma to distinguish it from peripheral neurofibroma, comprises the second largest number of tumors of the spinal cord in the series of 312 cases. Although this section is devoted to extradural tumor, it may be well, in taking up the neurofibromas, to take a broader view. In the entire series of 312 cases there were 68 cases of perineural fibroblastoma in which the growth originated from the spinal nerves and was found to be growing extradurally, intradurally and intramedullary. Fifty-two of the 68 tumors were found to be attached to the nerve roots within the dura, and did not involve the spinal cord except by compression. In 3 cases the tumor was shaped like a dumb bell; one part was attached to the nerve roots outside the dura, and extended through the intervertebral foramen to the other portion of the tumor, that lay outside the vertebral canal. In 2 cases the neurofibroma had developed within the spinal cord. The origin of these intramedullary tumors is rather difficult to understand, but recently I reported a case of neurofibroma of the spinal cord in which the tumor was buried in the cord but was easily enucleated. These perineural fibroblastomas arise from the perineural or endoneural connective tissue which invests the fasciculi and fibers, and some authorities, such as Roussy, Lhermitte, and Cornil have classified them with the gliomas. Penfield has proved conclusively by differential stains that they are fibroblastic in structure. Microscopically, the structure is characteristic. There is palisading and parallelism of nuclei, and a tendency to form nuclear eddies and streams. These tumors are benign and encapsulated, and may be completely removed. The prognosis following complete removal of such benign tumors depends on the amount and duration of compression of the spinal cord.

Fibrochondroma (6 Cases) and Chondroma (3 Cases): According to Boyd, cartilaginous tumors of bone occur in the course of the period of growth of bone, and tend to cease developing when that period is over. They may also occur in bone which arises chiefly from portions of cartilage which probably have become misplaced through some error of development. The extradural chondroma causing compression of the spinal cord usually arises from the intervertebral disks; Dandy has reported 2 cases of detached intervertebral disks protruding into the spinal canal and causing compression. Ewing stated that trauma and inflammation are usually the causes of chondroma, and trauma is not infrequently reported as preceding chondroma and fibrochondroma. These tumors are sometimes diagnosed preoperatively by means of roentgenologic examination, and may be difficult to distinguish from the roentgenologic picture of giant cell tumor of bone because of the tendency to form cyst-like cavities. The

cases of fibrochondroma and chondroma mentioned in this paragraph were distinguished by the predominance of fibroblastic tissue around the chondromatous cells.

Tuberculoma (4 Cases): Tuberculomas of the spinal cord and its membranes seldom occur unaccompanied by tuberculous disease of the vertebrae. Tuberculous infection may remain limited to the dura, producing pachymeningitis, or may pass to the pia and arachnoid, producing leptomeningitis. If the pachymeningitis is secondary to vertebral disease, the tubercles at first are external and the inner surface of the dura may suffer secondarily. Tuberculosis of the pia arachnoid may be of hematogenous origin, the disease beginning about the vessels of the pia. Compression of the spinal cord caused by a tuberculoma, unassociated with vertebral involvement, as evidenced by roentgenologic examination, is very difficult to distinguish from other types of compression of the spinal cord. Exploration was performed in these cases under such circumstances of difficulty in diagnosis, and the condition was found to be tuberculosis of the dura, extradural in situation, and taking the form of tuberculous pachymeningitis.

Hemang oma (3 Cases) and Hemangioendothelioma (5 Cases): Vascular tumors of the spinal cord which occur extradurally arise from vessels which normally are found lying extradurally. On gross examination it is often difficult to distinguish between hemangioma and hemangioendothelioma, and such distinction can be made only by microscopic examination. Hemangiomas are benign, but hemangioendotheliomas may be either benign or malignant, depending on the type of cell most prevalent. Tumors of this type are usually of slow growth, as evidenced by supporting connective tissue stroma. An extradural hemangioma was removed from the cervicodorsal region, and a hemangioendothelioma found extradurally was removed from the seventh dorsal segment.

Foreign Body Giant Cell Tumor (4 Cases); For many years, this condition was diagnosed as giant cell sarcoma and was treated as a malignant neoplasm. It has also been called myeloid sarcoma. According to Ewing, Nélaton first fully described this tumor as a benign process in bone, emphasized its red, jelly-like appearance, noted its capacity to absorb bone, and established its benign course and the reasonableness of conservative treatment. The reputation of the tumor as a malignant growth probably arises from the fact that repeated local irritation, n the form of curettage, sometimes results in the development of malignant spindle-cell sarcoma. Barrie considered that the process was inflammatory and not neoplastic, and that it was a chronic inflammatory, hemorrhagic osteomyelitis. A distinct relationship seems to exist between giant cell tumor and osteitis fibrosa cystica, although this has never definitely been verified. A giant cell tumor may be periosteal or medullary, and it is the medullary type which is found involving the vertebrae. The gross appearance is characteristic, and must be carefully distinguished from that of malignant hemorrhagic endothelioma. The tumor is very vascular and suggests young granulation tissue. It is dark red, and soft. According to Boyd, microscopically the tumor is made up of spindle-shaped cells without hyperchromatic nuclei, and in addition, the characteristic giant cells which gave the condition its name, are found. These may be very numerous in one part of the mass, and scanty or absent in another. The giant cells are characteristic of foreign body giant cells in that they possess small, oval nuclei which are situated toward the center of the cell and not around the periphery or at one end, as is commonly seen in tuberculosis. The cytoplasm is opaque and stains deeply. These cells, whose function is probably destructive, are regarded by some as osteoclasts, but the appearance is probably more characteristic of endothelial cells.

Unclassified Tumors: In 2 cases the tumors were not classified.

INTRADURAL TUMORS

Intradural extramedullary tumors of the spinal cord (156 cases) comprised approximately 50 per cent of the present series of tumors that compressed the spinal cord. Fortunately they were, for the most part, capable of being removed at operation. Neurofibromas and meningeal fibroblastomas predominated and contributed to the entire series a background of favorable prognosis.

Fibroma (3 Cases) and Fibrosarcoma (2 Cases): These fibroblastic tumors which lay within the dura and did not involve the spinal cord, except by compression, were primary tumors and were completely removed at operation. They presented the usual microscopic appearance, and the malignant changes were those which occur in tumors of similar structure elsewhere.

Endothelioma (75 Cases): Arachnoid Fibroblastoma; Meningeal Fibroblastoma; Leptomeningioma: The terminology applied to these meningeal neoplasms has resulted in a rather confused nomenclature. Until 1921, they were commonly considered as dural endotheliomas. At that time, Mallory demonstrated that the "type cell" of the dural endothelioma lays down fibroglia, although in the more rapidly-growing regions none of these fibers can be found. Consequently, he proposed the name arachnoid fibroblastoma. Elsberg, in 1925, pointed out that in the spinal cord these tumors are sometimes attached to the dura but have no attachment to the arachnoid, suggesting the possibility that in such cases they arise from the cells on the under surface of the dura which correspond to those opposed to them in the arachnoid. Learmonth, in 1927, in a comprehensive monograph emphasized the outstanding characteristic of these tumors and called them leptomeningiomas. Virchow observed the prevalence of "sand bodies" in these tumors, and designated them as psammomas, due to concretions or psammoma bodies. Later they were called endothelial psammomas because of the microscopic picture, in which neoplastic nuclei were seen. The nuclei are usually fat and oval, and often arranged in columns, or more typically in whorls, which may have as their center a collagen fiber, a small vessel, or no demonstrable structure. In the whorls or elsewhere in the tumor, small concretions of calcium often appear which are similar to the corpora amylacea found in other parts of the body. Penfield, in a recent study of fibroblastoma and arachnoid fibroblastoma, stated that in view of the fact that there may be no demonstrable attachment of the arachnoid and that the tumor indubitably is of fibroblastic structure, a more satisfactory terminology would be meningeal fibroblastoma. These tumors are found predominately to be intradural but extramedullary, and to form the largest single class of tumors of the spinal cord. The 75 meningeal fibroblastomas were found at operation and were removed. Fortunately, in view of their numerical incidence, they carry an excellent prognosis postoperatively. Although benign and encapsulated, these tumors have a tendency to recur if their dural attachment is not removed at the time of operation.

Hemangioma (7 Cases) and Varix (4 Cases): Tumors of vascular origin which arise from the vessels within the dura may be grossly neoplastic in character, or may assume the proportions of varicose veins. The former have been considered with extradural hemangiomas. The latter may occur with or without an associated tumor but a diagnosis of intradural varicose veins can be made only after exhaustive examination at operation because it has been demonstrated that compression of the spinal cord due to tumor causes vascular stasis and enlargement of the vessels. When varicose veins are found causing compression of the spinal cord, the decompression resulting from laminectomy usually relieves the clinical symptoms, but when possible the veins should be ligated and removed. The intradural hemangiomas were removed, and were found to have the characteristic microscopic picture. In the

4 cases of varix, tumor was not associated with the compression of the spinal cord.

Glioma (5 Cases): On microscopic examination these tumors proved to be gliomas. These tumors were intradural and did not seem to have any connection with the spinal cord itself, but they probably were extensions from the spinal cord proper, although no evidence of an associated intramedullary tumor could be found. This type of tumor will be considered with the intramedullary group.

Neurofibroma (52 Cases): Second only to meningeal fibroblastoma in number, intradural neurofibromas were found to be the cause of compression of the spinal cord and were removed at operation. Fortunately, also, although numerically predominant, they resemble meningeal fibroblastomas in being benign and encapsulated. On gross examination their appearance is characteristic. The microscopic appearance has been considered under neurofibromas occurring extradurally.

Ependymoma (6 Cases): Tumors of the spinal cord found attached to the fibers of the cauda equina have proved tremendously difficult to classify pathologically. Elsberg referred to them as giant tumors of the cauda equina, and described them as growing to a large size among the nerves. In this series of cases caudal tumors were found to be either attached to the nerves themselves or to the filum terminale. When, on gross examination, they did not involve the conus medullaris, they were classified as intradural extramedullary tumors and were identified microscopically as hemangioma, ependymoma, or neurofibroma. The hemangiomas and ependymomas are similar in their gross characteristics; both of them are found attached to the filum terminale and both may be completely removed. The 6 tumors found proved on microscopic examination to be similar to the intramedullary ependymomas and evidently had their origin in the filum terminale. On gross examination, they were found to be the type of tumor which could be completely removed by excising the filum terminale above and below.

Fibrochondroma (2 Cases): These tumors were similar in structure, microscopically, to the extradural group of tumors. The exp anation of these tumors occurring within the dura is rather difficult, unless the theory is accepted that they were heterotopic or extended through the dura. No evidence of extradural chondroma could be found in either case, however. The tumors were benign and encapsulated, were attached to the dura, and did not involve the spinal cord except by compression.

INTRAMEDULLARY TUMORS

The intramedullary group of tumors (89 cases), fortunately is much smaller than the extramedullary group, and although most of them arise within the canal and infiltrate the cord, occasionally a benign encapsulated tumor is encountered which can be removed.

Glioma (25 Cases): The predominant neoplasm in the present series of intramedullary tumors was found to be a glioma arising from neural elements of the cord. These gliomas are prone to infiltrate the cord, although they may be separated from the surrounding tissue by a region of softening. Although only 25 tumors were demonstrated microscopically to be gliomas, the majority of those which are listed with the miscellaneous and unclassified growths were undoubtedly gliomatous. In some instances, these tumors were partially extruded from the cord following longitudinal section. One proved to be an intramedullary vascular glioma which had extended outside the cord and which had been partially extruded before operation.

Ependymoma (19 Cases): These tumors originate from the ependymal cell of the central canal of the spinal cord, and differ microscopically from gliomas in that the cells are flat and elongated.

Neurofibroma (3 Cases), Meningeal Fibroblastoma (2 Cases), Fibroma (2 Cases) and Fibrolipoma (1 Case): Intramedullary

tumors rarely are encapsulated and susceptible of being enucleated, but of all of the tumors mentioned in this paragraph, some of the tissue could be removed, and in a few cases complete extirpation was possible. Therefore they should not be classified as true intramedullary tumors. The microscopic structure has been considered previously.

Sarcoma (2 Cases) and Carcinoma (2 Cases): Metastatic tumors of the spinal cord have been considered with the extradural group. Lesions primary to those mentioned in this paragraph were not demonstrable. The tumors were diagnosed microscopically. Prognosis is similar to that in other cases of metastasis of malignant growths.

Cysts (6 Cases): Intramedullary cysts of the spinal cord are relatively rare. They may cause changes in the cord similar to those which follow compression by solid neoplasms, and are difficult to distinguish preoperatively. These cystic cavities within the cord, indistinguishable in their clinical characteristics from solid neoplasms, are usually gliomatous although it is sometimes difficult to demonstrate any tumor tissue in the walls of the cysts. In 1 case of this series, on clinical examination there was an indeterminate level of sensory disturbance with a subarachnoid block. Lipiodol was injected intrathecally, and a typical dome-shaped shadow of a tumor of the spinal cord was demonstrated in the roentgenogram. At the level of the shadow, an enlargement of the spinal cord was found at operation. The lesion did not have the gross characteristics of an intramedullary tumor, but seemed to fluctuate; when aspirated, yellow fluid was obtained but tumor tissue could not be found, even after dorsal incision in the spinal cord had been made.

Consideration of cysts of the spinal cord would not be complete without some reference to syringomyelia. This condition can usually be distinguished clinically from tumor of the spinal cord, but symptoms of compression of the spinal cord associated with subarachnoid block of the cerebrospinal fluid may so mask the differential diagnostic signs that exploration is resorted to in order to determine the underlying pathologic changes. Relief may follow the release of the fluid and the associated compression.

There were 27 miscellaneous and unclassified tumors.

SUMMARY

Tumors of the spinal cord, if diagnosed and removed early in their development, can be permanently cured. Any condition which produces compression of the spinal cord may simulate tumors of the spinal cord.

In order to correlate more fully the relation of clinical, surgical, and pathologic aspects of compression of the spinal cord, material gathered from cases reported at The Mayo Clinic from 1912 to 1929 has been analyzed. In view of the difficulty in nomenclature of tumors of the spinal cord, the terminology was confined to an accepted classification, and the microscopic examination was made by means of frozen sections stained with hematoxylin and eosin.

Of 312 cases analyzed, 223 tumors were found which did not involve the spinal cord except by compression; these were classified as extramedullary, and were divided again into 156 intradural and 67 extradural tumors. There were also 89 tumors which involved the spinal cord and were classified as intramedullary.

Included in the group of 67 cases of extradural tumors compressing the spinal cord were lesions arising from bone, intervertebral disks, extradural fat, spinal nerves, and blood vessels, as well as unsuspected metastatic malignant lesions. A preoperative diagnosis of bony extradural lesion may often be made by roentgenologic examination; likewise, it is possible to make a presumptive diagnosis of metastatic malignant lesion when the primary lesion can be determined.

The intradural extramedullary series of

tumors comprised the largest group, and fortunately carried the most favorable prognosis. These lesions take their origin from the fibroblastic structures of the meninges and the vessels of the meninges, or they are projected into the subarachnoid space from without the dura or from within the spinal cord. The 2 types of tumor predominating are the endothelioma, or meningeal fibroblastoma, and the neurofibroma. In this series, about half of the intradural extramedullary tumors proved to be endotheliomas, and about a third were neurofibromas.

In analyzing the intramedullary lesions, 89 cases were reviewed. Tissue was available in only 62 cases. Tumors arising from the cord and comprising the group of gliomas predominated, but also benign encapsulated tumors which were capable of complete removal were found. In a number of cases in which tissue was not removed, palliative relief was obtained by means of decompression, coincidental with laminectomy.

In view of the fact that laminectomy can be performed with minimal risk, exploration can be carried out in many atypical cases of compression of the spinal cord for palliative as well as for diagnostic purposes. In a very high percentage of cases of compression of the spinal cord, a differential diagnosis between inflammatory and neoplastic lesions can be ascertained preoperatively by means of roentgenologic examination, complete neurologic study including examination of the cerebrospinal fluid, and the use of lipiodol when indicated. But the exact pathologic nature of the underlying cause of compression is rather difficult to determine, and this pathologic analysis furnishes evidence of the multiplicity of lesions that can be encountered at operation.

TABULATION

TISSUE CHANGES THAT CAUSE COMPRESSION OF THE SPINAL CORD

Extrameningeal	Arch of vertebrae	Hypertrophic osteitis	
		Benign giant cell tumor	
		Osteoma	
		Chondroma	
	Body of vertebrae	Carcinoma, metastatic	
		Osteosarcoma	
		Benign giant cell tumor	
	Intervertebral disk	Chondroma	
		Fibrochondroma	
		Fibromyxochondroma	
	Extradural fat	Lipoma	
		Lymphosarcoma	
		Fibrosarcoma, metastatic	
		Hypernephroma, metastatic	
	Spinal nerves	Neurofibroma	
	Blood vessels	Hemangioma	
		Hemangioendothelioma	
Meningeal	Extradural	Tuberculoma	
		Fibroma	
		Pachymeningitis	
	Intradural	Endothelioma (meningeal fibroblastoma)	
		Hemangioma	
		Neurofibroma	
		Cystic arachnoiditis	
		Varicosity of vessels	
Medullary	Cord	Fibroma	
		Ependymoma	
		Glioma	
		Angioma	
		Endothelioma	
		Fibrolipoma	
		Hemangioma	
	Intramedullary	Cysts, including syringomyelia	
		Abscesses	
		Malignant metastatic growths	

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*Continued from p. 265.

PRACTICAL PROCTOLOGY*

SAMUEL G. GANT, M.D.

NEW YORK

PROCTOLOGY occupies a prominent place in the Biblical, ancient and modern history of medicine. Until recently the treatment of rectal affections rested largely in the hands of ignorant advertising itinerants because of the brutal and unsatisfactory manner in which they were handled by regular physicians and surgeons.

During the last three decades rectal specialists have perfected their technique to a high degree so that today anorectal affections are accurately diagnosed and quickly prepared and operated upon under local anesthesia without confining the patient to bed for more than a few days or causing the agonizing postoperative pain that formerly followed operations for hemorrhoids, fissures and fistulae. As a result of these advancements quacks are becoming extinct and anorectal diseases are being more frequently and intelligently handled by the regular profession.

Hemorrhage, incident to vomiting, straining, and pulling off of dressings after ether, is avoided by infiltration anesthesia and severe postoperative pain is prevented by substituting thin drains for thick packing and mild stimulants (silver nitrate 6 per cent or ichthyol 15 per cent) for stick silver and copper in the treatment of wounds. Hemorrhage is also avoided by the use of mineral oil to soften and lubricate stools instead of cathartics which liquefy them to the patient's discomfort.

General anesthesia may be employed when operating for cancer, stricture, deep abscesses, complicated fistulae, high polyps, imbedded foreign bodies, complete incontinence, extensive procidentia recti, abdominal complications and surgical procedures where the nature and extent of cutting cannot be determined beforehand.

Spinal anesthesia is effective in these conditions but sacral or caudal anesthesia should be discarded since all minor rectal operations can be painlessly performed under infiltration anesthesia in less time than it takes to desensitize the parts in the manner described.

Local Anesthesia: The writer has employed infiltration anesthesia for twenty-five years and performed over 15,000 operations under it without a single serious complication or dangerous postoperative hemorrhage.

Local anesthesia is always effective and obtained in about ten seconds when the operation field is distended with the solution until white with or without adrenalin. Different drugs are useful but novocaine 1 per cent is satisfactory because it is reliable and found in all operating rooms. Quinine and urea are contraindicated since when not followed by sloughing they cause induration of tissues and slow healing.

Infiltration (pressure) anesthesia is linear for fistulae and skin incisions but made directly into the parts when hemorrhoids, fissures, tumors, polyps and anal papillae are removed; one or more injections are employed depending on the operation.

The writer employs local anesthesia in the following cases which constitute more than 80 per cent of anorectal diseases: Internal protruding, bleeding, capillary, combination, external, cutaneous and thrombotic hemorrhoids; fissures, ulcers, single and multiple, superficial long and short fistulae; procidentia recti (first and second degree), cryptitis, hypertrophied anal paillae, marginal, submucous and ordinary ischiorectal abscesses; polyps, low strictures, foreign bodies, constipation incident to sphincteralgia, hypertrophy of

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the levator ani muscle or narrow anal canal, incipient anal epithelioma, perianal cysts, tumors and condylomata; pruritus ani, sacral dermoids and fecal incontinence.

Under infiltration anesthesia the writer has often performed exploratory celiotomy, colostomy, appendicostomy, cecostomy, ileostomy, sigmoidopexy, colopexy and other abdominal operations including breaking up of adhesions, straightening Lane's kinks, dividing Jackson's membrane, draining an obstructed bowel and closing appendiceal and cecostomy openings following the cure of chronic ulcerative colitis.

A 2 oz. metal syringe having a goose-neck attachment and strong screw-on needles of variable lengths are required in the successful production of local anesthesia.

Hemorrhoids: All types of hemorrhoids are operated on under local anesthesia without adrenalin or divulsion of the sphincter which can if desired be accomplished by superficial infiltration of the perianal region.

Internal hemorrhoids are separately exposed through an anoscope having a slanted end, injected until distended and white, drawn down with blunt forceps, dissected upward, ligated at the upper attachment of the pedicle and excised, each tumor in turn being treated likewise.

The ligature is the operation of choice because it is quickly performed and post-operative hemorrhage is rare. Redundant skin is removed with the hemorrhoid or separately by a v-shaped cut pointing in the rectum. Should there be oozing bleeding is controlled by the insertion of a vaseline covered gauze plug through the anoscope.

External thrombotic tumors are infiltrated and incised and the clot evacuated following which skin edges are excised and the wound is packed with a gauze pledget to control bleeding. Cutaneous piles and skin tabs are individually injected, caught with forceps and removed with scissors.

These operations are painless except for a twinge from inserting the needle; post-operative pain is nil when morphine grain ¼ is given hypodermically fifteen minutes previous to operation and repeated later should pain recur.

Hemorrhage, which is rare following local anesthesia operations, is prevented by a wedge-shaped compress snugly held in place by a tightly adjusted T-binder. Polyps are ligated and excised following novocainization at their attachment to the mucosa. Hypertrophied anal papillae are caught and snipped off with scissors and inflamed crypts are hooked up and excised following infiltration without the patients going to the hospital.

Anal fissures, the result of a narrow anal canal and constipated stools, the most painful of all anorectal diseases, are characterized by their location in the posterior commissure, slit-like appearance, accompanying spasm of the levator ani and sphincter muscles that induce excruciating pain during and following stool and blood streaks upon the feces. Occasionally they are healed by restricting the diet, softening stools with fruits, oils and laxatives and applying silver nitrate 6 per cent or ichthyol 15 per cent. The practice of cauterizing fissures with stick silver or copper is to be condemmed because of resulting terrific pain and delayed healing. Sphincteric divulsion gives only temporary relief and should be abandoned.

The writer's anal canal splitting operation is curative and prevents recurrence, since it arrests muscular spasms, widens the anal canal and provides for free evacuations. His technique consists in making a 1½ in. incision in the posterior median line through the fissure, perianal skin (to insure drainage), sphincter and fibers of the levator ani muscle following linear novocaine infiltration. Subsequently following swabbing a gauze drain is daily inserted in the wound which stimulates healing and leads to widening of the rectal outlet.

Anorectal ulcers, which are superficial, irregular-shaped and accompanied by a discharge, are often cured with ichthyol

5 per cent enemas, touching them individually with silver nitrate 8 per cent, and procuring semi-solid evacuations with oils.

tion of a probe to define the tract and openings; then following removal of the probe and introduction of a curved probe

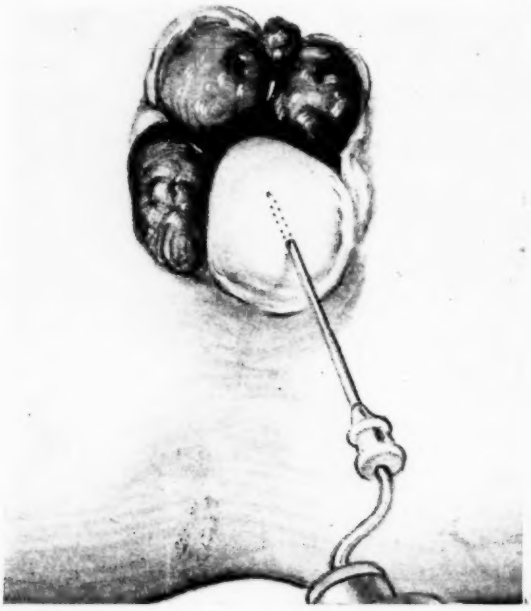

FIG. 1. Method of infiltrating extruded hemorrhoids preceding dissection from their base, ligation and amputation.

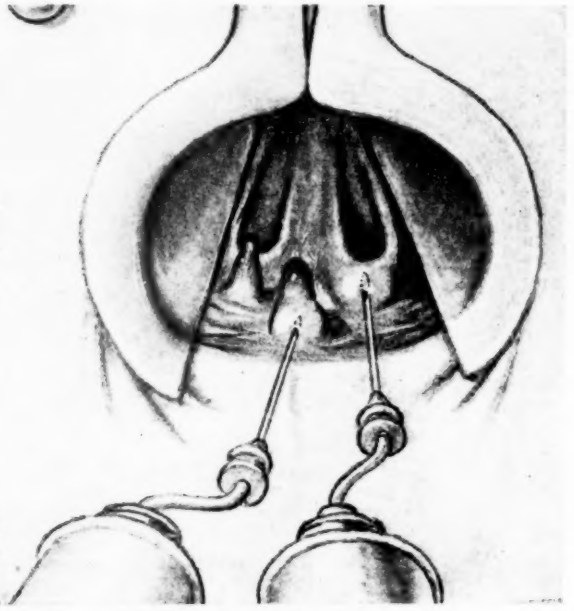

FIG. 2. Papillae and inflamed crypts are caught and excised following infiltration.

When ulcers are deep and sensitive they are curetted under local anesthesia and irritable muscles are divided posteriorly following which the wound is cleansed and drained as after fissure operations. Colonic ichthyol 5 per cent or silver nitrate (grains 8 to 1 qt.) irrigations are prescribed for high lesions when colitis is a complication.

Subcutaneous, submucous and other minor perianal abscesses are freely incised, curetted and drained under novocaine, but deep extensive ischio-rectal, perirectal and pelvirectal pus collections are taken care of under gas oxygen since infiltration anesthesia is painful and unsatisfactory.

Fistulae are treated by division under infiltration anesthesia since excision usually fails and the injection method is useless. General narcosis is employed for complicated fistulae but local anesthesia has proved satisfactory in 80 per cent of the writer's operations whether sinuses were single or multiple. The technique is simple and consists in linear infiltration of skin and overlying tissues following introduc-

pointed steel groove director the sinus is divided which may or may not necessitate severing the sphincter depending on whether or not the tract runs below it or just beneath the mucosa and skin.

The sinus is easily dissected out but this is unnecessary since a cure follows simple incision when the wound is daily swabbed and drained (not packed). Postoperative fecal incontinence is rare when a gauze pledget is daily inserted instead of tight packing which destroys granulations. It keeps the muscle ends apart and leads to the formation of sulcus through which feces involuntarily escape. Multiple sinuses are in turn divided but the main tract entering the rectum posteriorly in the median line is incised last. Gauze is a sufficient stimulant but when healing is sluggish mercurochrome 2 per cent, silver nitrate 6 per cent or ichthyol 15 per cent applications are employed, stick silver and copper being used only to destroy exuberant granulations. Tuberculous fistulae are curable in a similar manner except when the

patient's vitality is markedly reduced by phthisis.

Pruritus ani: Medication, sera, roentgeno-

Fig. 3. Showing local anesthesia division operation for fistulae.

therapy and the subcutaneous injections of alcohol, quinine and urea or hydrochloric acid are unsatisfactory and best results are obtained from the undercutting operation described later which liberates entangled nerve ends.

By the use of a long needle perianal skin and anal mucosa are infiltrated with novocaine; through four right angle ½ in. incisions made equidistant to each other and 1 in. from the anus, blunt pointed scissors are introduced and all nerves are severed from the involved skin area and anal canal mucosa; finally gauze drains are inserted through the four original incisions. Proctitis, hemorrhoids, ulcers or other conditions causing a discharge must be corrected, otherwise pruritus may recur.

Prolapsus ani (first and second degree) is corrected by seizing, ligating and amputating several areas of mucosa following novocainization (Fig. 5). This causes adhesion of mucosa to the muscular coat and subsequent shortening of the rectum through resulting cicatrices. An elaborate plastic operation is required for third degree procidentia recti.

Rectal Constipation: Delayed and incomplete evacuations are frequently due to anorectal lesions, viz.: fissure, hemor-

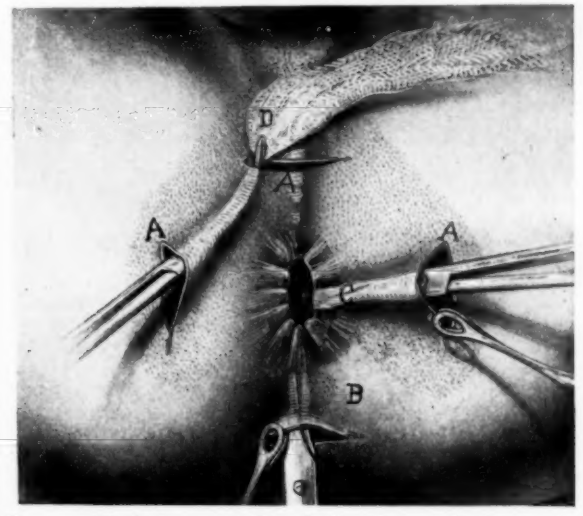

Fig. 4. Technique of Gant's local anesthesia undercutting operation for pruritus ani.

rhoids, fistulae, hypertrophied papillae, etc., which block the bowel or cause sphincteric spasm the treatment of which has already been outlined. Most often rectal constipation is induced by hypertrophy of the rectal valves, evator ani or sphincter muscles or narrowing of the anal canal. Rectal valves are divided with the writer's valve clips. When obstipation is due to thickening or spasms of the sphincter or levator ani muscles, or a contracted lower rectum, it is corrected and comfortable stools procured by infiltrating the rectal wall posteriorly, in the median line, and splitting the anal canal and muscles with a blunt pointed bistoury, and treating the wound as after fissure operations, a procedure which leads to permanent widening of the anal canal and regular movements.

Perianal cysts, tumors and sacral dermoids (pilonidal cysts) are destroyed under local anesthesia by infiltrating overlying integument, dissecting them out or incising, curetting and draining cavities where they have become infected; but unless the entire sac and contents are removed a second operation will be required.

Cicatricial and other strictures located

in the lower 3 in. of the rectum may be divulsed or preferably divided at several points following novocaine infiltration but

Fig. 5. Writer's local anesthesia multiple ligature operation for procidentia recti.

higher stenoses necessitate general narcosis and excision or colostomy.

Ulcerative Colitis, Appendicostomy and *Cecostomy:* Frequent fluid evacuations containing mucus induced by gastrogenic, neurogenic, and gastroenterogenic disturbances come within the domain of general medicine but when the colon and rectum are extensively ulcerated, the result of catarrhal, tuberculous, amebic, balantidic, helminthic, flagellate, parasitic, gonorrheal or syphilitic infection and the patient is exhausted because of indigestion, frequent evacuations, abdominal pain, gas distension and hemorrhages, the case is surgical since dieting, medication and rectal irrigations benefit the patient only temporarily. In such cases colonic organisms aggravate the ulcerative process in all cases.

Patients afflicted with severe chronic colitis are anemic, nervous, show a marked loss in weight and are discouraged because of having been treated by different physicians without relief. These sufferers readily respond to appendicostomy and cecostomy plus through and through colonic medicated irrigations and in more than 300 cases treated by the writer a cure was obtained in over 90 per cent and all patients rapidly gained in weight and morale. In 10 per cent not cured but greatly improved

Fig. 6. Writer's stab-wound appendicostomy and subsequent colonic through and through irrigation.

infection was due to tubercle infection complicated by phthisis, Balantidium coli or some obscure complication.

Appendicostomy and cecostomy openings were quickly, painlessly and safely closed extraperitoneally in the office or hospital by ligating and amputating the freed appendiceal stump or fistulous tract at its cecal juncture following infiltration of the skin and deeper structures with novocaine and approximating wound edges with interrupted stitches.

Subsequent to appendicostomy and cecostomy patients are permitted a regular diet excepting raw fruits and rough vegetables and advised to partake freely of baked potatoes. Through and through colonic quart irrigations of ichthyol 5 per cent are employed twice daily unless stools contain considerable blood when silver nitrate irrigations (5 grains to a quart) are employed until bleeding ceases. Bowel flushing is continued until stools are normal and the patient regains his digestion morale and weight when the appendiceal or cecal opening is closed.

Appendicostomy and cecostomy are pref-

erable to enterostomy and colostomy because the latter are not effective and subject the patient to the annoyance of an artificial anus. Appendicostomy and cecostomy are dependable but appendiceal irrigations are preferable since appendicostomy is less often complicated by superficial infection and is employed unless appendectomy preceded the colitis. The mortality was 2 per cent in 200 and nil in the last 100 cases of appendicostomy and cecostomy performed by the writer.

The technique of appendicostomy is simple, viz.: through a right rectus incision the appendix after being located is brought out through a stab wound (Fig. 6) and sutured to the skin following which it is amputated and the irrigating catheter introduced. In cecostomy after exposure through a similar incision the cecum is punctured, a catheter is inserted and attached with a purse-string suture and the wound closed with interrupted linen sutures.

In both operations the cecum is adhered to the parietes by suspension sutures tied across rubber tubings on either side of the appendiceal stump or catheter. This procedure is important since it permits extraperitoneal closure of the irrigating aperture under local anesthesia when the patient is well.

Anorectal Cancer: Eighty per cent of anorectal cancers involve the rectum of which 75 per cent are in the bowel and 5 per cent at the anus. Epitheliomas (squamous-celled) attack the anal margin while carcinomas (cylindric-celled) are located in the rectum proper and may be encephaloid (soft), scirrhus (hard), colloid (gelatinous) or melanotic (pigmented).

Epitheliomas begin as wart-like excrescences with inflamed ulcerated edges and cause constipation, excruciating pain, sphincterismus, offensive discharge, painful defecation and slight loss in weight but rarely cachexia.

Carcinomas are differentiated by their hard lumpy feel, rapid loss in weight, cachexia, offensive mucopurulent secretion containing blood, constipation, straining and a feeling as if something was left in the bowel after defecation. These tumors are readily diagnosed by touch and inspection through the proctoscope.

Treatment: Suffering is mitigated by regulating diet and stools, alleviating pain with opiates and cleansing the bowel with irrigants. Deep *x*-ray applications often minimize pain and sometimes cause slight shrinkage of neoplasms but otherwise are unreliable.

Radium, occasionally effective in anal epitheliomas (skin) markedly increases pain when introduced into the rectum. One case of carcinoma involving the lower sigmoid was cured by projecting seeds into the tumor, but radium however used by the writer has in all instances failed to cure rectal carcinoma.

Operative Treatment: Rectal malignancy is a surgical disease and must be removed with adjacent fat and infected glands. Colostomy is employed to prevent obstruction and in excision cases where growths are in the upper sigmoid or colon and resection is impracticable. Good results follow radical operation and mortality is less than 5 per cent when movable tumors are removed by perineal excision as described later.

Cancers involving the lower sigmoid and rectum have been removed by perineal, sacral, vaginal and perineo-abdominal excision but the writer employs only the first-named.

Perineal Excision: In 50 recent cases perineal excision was employed exclusively and little difficulty was encountered in extirpating high and low rectosigmoidal growths without removal of sacral or coccygeal segments or establishing an artificial anus. In 80 per cent operation was performed in less than half an hour and the bowel brought down and sutured in the anal region causing but slight or no shock.

Briefly described the following is the technique employed by the writer:

First step: Skin and rectum having been swabbed with iodine the anus is closed by a

linen purse-string suture. *Second step:* The terminal rectum is freed by perianal incisions carried through skin and subcutaneous fat and the writer's safety pin retractor is inserted or the bowel is clamped with heavy curved pressure forceps which serve for manipulative purposes.

Third step: Perirectal and the levator ani muscles are hooked up with finger and severed with blunt scissors which loosens the lower 2 in. of the rectum. *Fourth step:* The bowel is freed anteriorly from the prostate or vagina by blunt dissections. *Fifth step:* Higher perirectal muscles, ligaments and fascia are in turn divided using finger tip as guide and scissors dissections carried towards the bowel anteriorly and laterally and from the gut posteriorly (to avoid vessels). *Sixth step:* Having controlled bleeding with boiling hot water gauze packs and ligatures, encircling peritoneum is severed in similar manner. *Seventh step:* The bowel is drawn downward from 3 to 15 inches as high restraining fascial and ligamentous bands are severed. *Eighth step:* The gut is amputated with cautery ligated about 1 in. rubber tubing and anchored by linen sutures at the anal site following the introduction of anterior and posterior drainage packs. *Ninth step:* Wound edges are approximated with interrupted linen sutures. *Final step:* A thick firm gauze compress is placed over the wound and held in place by a snugly adjusted T-binder through which the rubber tube projects that gas and feces may escape without soiling the wound.

Postoperative treatment consists in elevating foot of the bed, restricting diet to liquids and prescribing opiates to tie up the bowel and keep the patient comfortable.

The chief advantages of perineal over other excision procedures are: only a few moments are required, shock is almost nil owing to quick removal and method of controlling hemorrhage, the anus is located at the normal site, convalescence is shorter, the patient has almost complete control over solid stools, disgusting features of colostomy are avoided, pain from bone stumps is prevented and postoperative sequelae are rare.

Operative results for rectal cancer are remarkably good because metastases form slowly and in the writer's cases cures have occurred as frequently after perineal as after the combined operation. In 300 cancers of the lower bowel the sigmoid or descending colon was involved in only 5 per cent and following 200 rectosigmoidal excisions recurrence was observed in the sigmoid in but 2 cases.

From this experience the writer is convinced the combination operation with colostomy should be abandoned in favor of perineal excision as it is evident sigmoidomesocolonic glands are seldom responsible for recurrence here though enlarged (inflamed) at time of operation.

HYPERPLASTIC PROCTITIS

(RECTAL GRANULOMA)*

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BUT few cases of hyperplastic proctitis have been reported; none were found in the American or English literature. Because of this, and the possibility of mistaking it for carcinoma, the following case is of interest:

History: Male, aged sixty, baker, married, entered Alexian Brothers Hospital, Chicago, on the service of Dr. Edward F. Hess, February 23, 1928, complaining of malaise, anorexia. pain in the left inguinal region and rectal trouble. This was a dull ache in the lower rectum, soreness and at times a dull pain when bowels moved, urgency, a blood-tinged purulent discharge which seeped through anus and occasional incontinence for liquid feces.

Past History: Married, wife living and well. No children. Previous illness: no significant previous diseases. Denies lues and gonorrhoea. Has had no operations. Health has been vigorous for his age until now.

Proctoscopic Examination: February 23, 1928. The mucosa of the last 2 in. of the rectum is replaced by a granulomatous tissue except for an irregular strip from ¾ to ½ in. wide of normal mucosa in the left lateral quadrant. The granulation tissue is paler than the normal mucosa above and is dotted with small red dots less than a millimeter in diameter. Thick yellow pus partially covers the granulations; this pus seeps through the anus, necessitating the wearing of a small pad. The granulating surface of the last 2 in. of the rectum is for the most part smooth but with nodular areas in places and especially at the upper (cephalic) edge of the involved area it is raised 3 to 5 mm. above the adjacent normal mucosa and has a nodular, polypoid configuration. To briefly describe the appearance: It is granular, paler than the normal mucosa, has an elevated irregular, rather nodular edge and is coated with thick yellow pus and mucopus. The red dots (capillaries) are not conspicuous; swabbing with cotton brings them out. On digital examination the tissue feels slightly firmer than the normal, except at the upper edge which is distinctly firmer. The scar of an old laceration can be felt through the anterior midline of the anus and up an inch in the rectum.

Present Illness: He states that he had been drinking New Year's Eve and that he wandered into a negro neighborhood. While passing a house he was seized by a big negro and an accomplice who dragged him inside and subjected him to sodomy. (Note: This may be the fanciful story of a pervert, but he maintains it.) The anus was sore afterward and when the bowel moved, painful; about two weeks later he noticed a discharge which seeped through the anus and a week after this the left inguinal glands became tender and enlarged. Seven weeks after the attack, February 23, 1928, he entered the hospital with a temperature of 100.8°F., pulse of 68, and respiratory rate of 20.

Course and Treatment: During his third week in the hospital a left inguinal gland suppurated and was incised and drained. Cultures from the pus were sterile. The inguinal wound did not heal well under the usual antiseptic measures and presented a rather granulomatous appearance. Because of the possibility of granuloma inguinale 5 intravenous injections of 1 grain of tartar emetic were given on alternate days. A biopsy report on the tissue from the inguinal lesion was: Infectious granuloma, not tuberculous. The inguinal condition gradually healed, but that in the rectum showed no improvement. Although repeated blood Wassermann tests and four dark field examinations were negative, the patient was given vigorous anti-syphilitic treatment by Dr. Hess as a therapeutic test. This consisted of 10 intravenous injections of 0.6 gm. neoarsphenamine, an average of 2 a week; 8 intramuscular injections of gray oil and 150 gr. of potassium iodide daily for ten days.

Laboratory Findings: Feb. 24, 1928: Blood examination: 4,070,000 erythrocytes, 7000 leucocytes. Differential: polymorphonuclears, 66 per cent small lymphocytes 28 per cent transitionals 6 per cent.

Feb. 10, 1928: Biopsy (Dr. Simonds:)

* Submitted for publication November 12, 1930.

a. Tissue from inguinal gland: Infectious granuloma, not tuberculous.

b. Tissue from rectum: Ulceration with

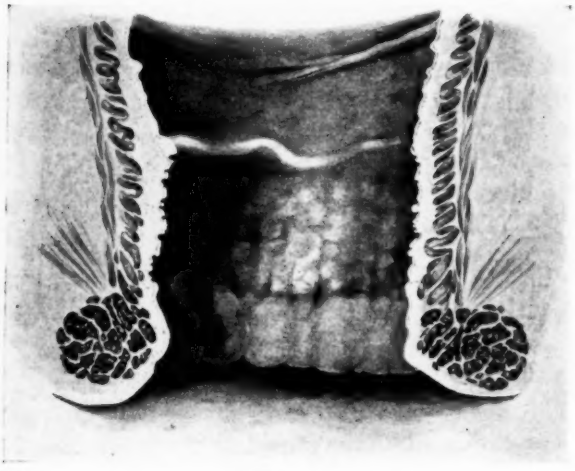

Fig. 1.

granulation with lymphocytes and plasma cells. No evidence of cancer or tuberculosis.

June 2, 1928: Biopsy (Dr. Simonds): Tissue from rectum. Surface squamous and the glandular epithelium in all sections is intact. The growth is composed of fibroblasts and round cells of various types. Diagnosis: Infectious granuloma.

He was discharged from the hospital with the rectal condition somewhat improved, May 4, 1928. In the year and a half since, his general health has been good. The rectal condition has remained much the same for this period, with the exception that it becomes more active for a few weeks in intervals of several months and the entire circumference of the bowel is now involved. In 1929 the granulomatous tissue was deeply fulgurated over the anterior half of the rectum but it promptly recurred and four months later there was no difference from the untreated half. The condition is slowly progressive, it has extended upward 1 to 1½ in. in two years. There is very little lessening of the rectal lumen and no tendency to stricture formation yet. A mucopurulent discharge continues and seeps through the anus, so a pad has to be worn, and occasionally there is incontinence for liquid feces.

On September 30, 1929, a third biopsy was made from the upper edge of the granulomatous surface. The histological findings are as follows:

A navy bean sized piece of soft, grayish pink colored tissue is submitted for examination. The sections show a well preserved rectal mucosa which contains hyperemic vessels and is densely infiltrated with lymphocytes, plasma cells, histocytes and leucocytes. The muscularis mucosa is split up by these infiltrations which extend into the deeper tissue where a marked fibrosis and hyalinization are present. The muscularis is apparently replaced by fibrous tissue. The vessels in these portions are dilated, but otherwise normal. The round cellular infiltrations do not show any direct connections to the vessels. There are small groups of large, vesicular cells found scattered in the tissue. The cytoplasm of these cells contains a very delicate pink stained network. The nucleus is round, moderately large and usually somewhat eccentrically located. Special staining for ameba after Jaeger is negative. Sections stained with polychrome methylene blue show in the submucosa occasionally large, mononucleated cells containing and surrounded by accumulations of very small round, gram-positive cocci which form sometimes short chains.

The bacteriological investigation of smears and cultures of the mucosa in dextrose bouillon, milk, Loeffler's serum agar and plain agar, showed the presence of gram-positive diplococci and short gram-positive rods. The normal flora of the intestine is mixed with a prevalence of gram-negative forms (B. coli). Cultures of excised tissue made by Dr. Ernest Pribram showed gram-positive bacteria.

The Frei test for lymphogranuloma inguinale, for which we obtained the antigen through the kindness of Dr. Frei,[1] was negative.

Comment

All the attempts to establish a definite etiology for the condition described have failed. The syphilitic origin has to be excluded due to the repeatedly negative Wassermann tests and the negative results obtained with antisyphilitic treatment and the negative histological findings. Granuloma inguinale can be dismissed as the specific treatment with tartar emetic was negative; Donovan bodies were absent in the smear and tissue and the histological structure in our case differs distinctly from that seen in this condition (Fischer and v.

[1] Frei. *Klin. Wchnschr.*, 4: 2148, 1925.

Gusnar.)[1] There is no evidence that we are dealing with lymphogranulomatosis inguinale as the Frei test, which according to this author is specific, was negative. The extremely prolonged course and the absence of Ducrey's streptobacilli is against a chancroid character of the lesion. There is also no support for a tuberculous etiology present. The rectal condition has therefore to be classified among the rather rare cases of chronic hyperplastic granulomatous proctitis of apparently non-specific origin. The characteristic feature of this condition in the replacement of the rectal mucosa by granulation tissue which shows but little tendency toward scar formation. The granulation tissue in which islands of surface epithelium may be present, may invade the muscularis and subserosa and may extend in these layers for large distances. Beside this granulomatous type of chronic proctitis there exists also a hyperplastic papillary one of tumor-like appearance (Siegmund).[2]

[1] Fischer and v. Gusner. *Beitr. c. path. anat. u. z. allg. Path.*, 81: 309, 1928.

[2] Siegmund. Handbuch der Speziellen Pathologischen Anatomie and Histologie. Springer, Berlin, 1929, 4: 3.

VASCULAR DISEASES OF THE EXTREMITIES

III. THERMIC GANGRENE*†

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THE occurrence of gangrene from exposure to cold is seen much more frequently in temperate zones than in those extremities of the earth where severe cold is always present. This lower incidence where one might expect it to be higher may be due in part to the adaptability of the organism to the environment, but for the greater part it can be accredited to education in prophylactic measures.

ETIOLOGY

Death of tissues from exposure to cold may be brought about in 4 ways: (1) reduction of the temperature of protoplasm to a degree and for a length of time incompatible with life; (2) ischemia; (3) reactionary hyperemia with transudation of serum into soft parts to compress the vessels and further cut off blood supply; (4) very rarely, thrombosis.

Factors which predispose to frostbite or gangrene are too numerous to review in detail. An extremity with an already impaired circulation is especially susceptible, but the normal one in an inactive state and clothed with moist socks or shoes may become rapidly frozen through both radiation and direct conduction.

PATHOGENESIS

On exposure to cold, the capillary bed and small vessels of the exposed part first dilate to produce an active hyperemia. This is in turn followed by cyanosis which shortly is followed by ischemia produced by vasoconstriction which persists and allows the cells to become further reduced in temperature. Under favorable conditions these changes may occur at temperatures considerably above freezing,[10] but with sufficient exposure to zero degrees centigrade, or below, the fluid elements of the tissues and blood may actually become frozen.

A part so exposed and properly treated may escape the formation of gangrene if the reduction in temperature and blood supply has not persisted too long. Not infrequently the institution of improper therapy causes gangrene. Heat too vigorously applied to the affected part favors the production of hyperemia and the transudation of serum into soft tissues which compress the vessels and further interfere with the blood supply to an already injured area.

That thrombosis may occur in vessels of a frozen part is not mentioned by most observers, but its occurrence was demonstrated by dissection in those cases reported by von Winiwater,[1] von Recklinghausen,[2] and Nagelsbach,[3] respectively.

Not infrequently infection plays an important rôle in the production or extension of gangrene when it is permitted to occur in already devitalized tissues.

SYMPTOMATOLOGY

Freezing of the tissues may be divided into 3 degrees, which are readily determined by inspection. These are: (1) erythema; (2) bleb or vesicle formation; (3) gangrene.

Upon exposure, the preliminary hyperemia usually gives rise to a prickly sensation, which serves as a warning to the initiated that soon there may follow a stage of vasoconstriction with absolute anesthesia. Explorers and others constantly exposed to severe cold frequently inspect one another for these ischemic, waxy-white patches, which usually occur on the fingers, toes, ball of the foot, heel, ears, nose, or wherever the skin is tightly stretched over bone.

If exposure is terminated early in the

* Presented before the Surgical Faculty, Tulane University, April 21, 1930.

† I. Arteriosclerotic Disease of the Extremities, and II. Erythromelalgia, appeared in the April, 1931, issue, pp. 32 and 40, respectively.

ischemic stage, there follows an intense reddening of the part accompanied by itching, prickly sensation and swelling. Recovery may follow, or there may develop bluish red, flat swellings or nodular elevations surrounded by a red zone representing chilblains.

If exposure is more prolonged, there results bullae, or vesicles on a reddened or violaceous skin. These contain a clear fluid and on rupture may heal easily or become the seat of an indolent ulcer.

With complete and prolonged freezing of a part, there occurs later, swelling, bluish red mottling or cyanosis, congestion, and persistence of anesthesia. With these manifestations, if circulation is not shortly reestablished, gangrene occurs. Distally, the gangrene may involve deep structures, including bone; but proximally, only the more superficial structures, and at the line of demarcation the skin, are involved.

Areas once frozen are subject to recurrences and following the shortest exposure to cold the sensations of burning or pricking in these areas become prominent.

PROGNOSIS

Meyer and Kohlschütter[4] believe that if areas of cyanosis, lividity, and anesthesia persist for a week or more, the part cannot be saved. A prognosis where factors may be so variable must be guarded. When ischemic areas are detected early and treated properly, they usually suffer no permanent damage.

TREATMENT

Education in prophylactic measures would do much to lessen the need of treatment. For those exposed to cold, the maintenance of a vigorous circulation and the wearing of loose, warm clothing should serve to prevent freezing. Proper clothing acts as a non-conducting air space between the skin and the outside air. If the clothing, whether it is wool or fur, becomes greasy or wet, the air is displaced from the meshes or hairs, respectively, and it becomes an excellent conducting medium. That grease, fats, and oils are relatively non-conducting is true; but air is certainly less conducting, and, therefore, the former should never be applied or be allowed to accumulate in clothing and should be used on the skin only when something is required to break the force of a strong wind on exposed parts.

The ideal foot gear is not obtainable. Waterproof shoes retain perspiration and those that permit ventilation allow absorption of water and moisture. Thus it becomes important to constantly inspect the feet in case of undue exposure and to change the socks and shoes immediately on cessation of activities.

The application or rubbing of snow on frozen parts is to be condemned, as it is not rational and may introduced micro-organisms into abrasions produced by its use. Measures to reestablish circulation quickly are undesirable as these produce a hyperemia and transudation of serum which favor mortification.

For primary frostbite the application of dry moderate warmth is desirable. This is probably most conveniently obtained by applying the frozen part to warm portions of the body. Gentle massage is of value in restoring circulation, but great care must be taken not to abrade the skin. Most cases should react to treatment of this sort within several hours.

For more severe cases immobilization and elevation of the affected part are important. If dry warmth cannot be conveniently applied, warm fomentations are satisfactory, provided that the solutions used are isotonic and thus not likely to produce an unfavorable reaction. As manipulations are undesirable, it seems probable that the application of cotton wool and a loose bandage should prove efficacious. If blebs form, these should be opened, but only under aseptic precautions.

The treatment as outlined has been entirely satisfactory in the hands of Mocklin[5] in various polar expeditions. More energetic means have been advocated by various authors. Noesske[6] and Weitig[7] make multiple incisions in order

to relieve impeded venous circulation. Wachtel[8] uses the roentgen ray, Bundschuh[9] combines multiple incisions with production of hyperemia, and others use contrast baths, exposure to the quartz light, etc.

When gangrene occurs, conservatism should be practiced at least to the extent of waiting for a definite line of demarcation before amputating. If a weight-bearing stump is not to be considered, a spontaneous amputation should be entirely satisfactory. Should infection occur, the resulting septic absorption or extension of the gangrenous area necessitates an early amputation.

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The American Journal of Surgery

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EDITORIAL

THIS issue marks the fifth anniversary of THE AMERICAN JOURNAL OF SURGERY under its present publishers. In celebration, we will indulge in the human traits of reminiscence and prediction.

With the coming of the age of efficiency and mass production, the art of soliloquizzing has gone largely into the discard as have the "asides" of the theatre. However, with Eugene O'Neil, the Editor will indulge in the old-fashioned pastime and confide to his readers that to publish or not to publish is a question of continual perplexity.

The size of the Journal has grown in the editorial, circulation and advertising departments. Where some years ago, it was a question of wondering from month to month how to fill the next month's quota of pages, the problem has now become a matter of selection.

Gratifying indeed to both Editor and Publisher is the continual stream of material that is coming to us from all parts of the country. Probably, no more sincere compliment could be paid to the Journal than this evidence of a definite desire to gain admittance to its pages.

There is, however, no rose without its thorns and we feel that out editorial sieve needs a finer mesh. It is very flattering to be flooded with manuscripts and it is the course of least resistance to accept most of the material that comes in. But times have changed. We are not going to be "snooty" but we are going to be critical indeed. We have on our staff specialists on every subject and each article will have to pass muster with the men who know the subject best.

It will not be necessary to have a

national reputation to get into the pages of THE AMERICAN JOURNAL OF SURGERY. In fact, we hope to have a hand in the making of some reputations in the future. But high standing in his community will be a *sine qua non* for the acceptance of any author's paper. The man of good standing who has really something to say and says it well, and in the fewest possible words, will have his material published promptly. The man who simply rehashes old material and the man who is writing to advertise himself will, as far as possible, be eliminated from these pages.

As we are not infallible, we ask the cooperation of our readers. If you feel that some article should not have been published, write us about it so that we may be guided by your suggestions.

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T. S. W.
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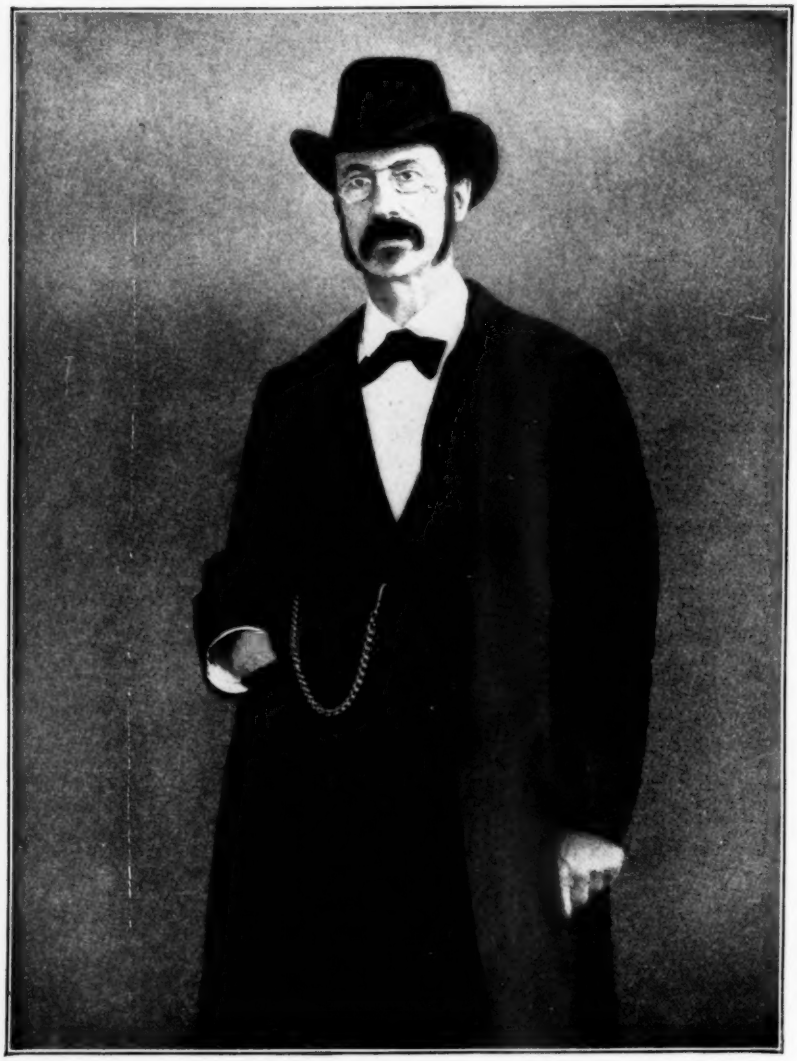

WILHELM HIS

[1831-1904]

"HIS' ZONE"

TO physicians His' name is associated with several eponyms: His' bursa, canal, rule, space. His son is known for such eponyms as His' band or bundle, and His' spindle. Hiss' stain was named after Philip Hanson Hiss, a New York bacteriologist who died in 1913.

Wilhelm His was born in 1831 at Basel, Switzerland. He will be known as one of the greatest embryologists of the nineteenth century. He did the best work of his day on the origin of tissues and the serial and morphological consideration of embryonic and adult organisms.

He came from a noted and distinguished family and had the advantages of an excellent education. His teachers were Johannes Müller, Robert Remak, Virchow, and Kölliker. His was professor of anatomy at Basel from 1837 to 1872. Through the influence of Carl Ludwig, he was appointed to the same chair at Leipzig. He kept this position the rest of his life.

He did important work on the normal and pathological histology of the cornea, the structure of the thymus glands, and the lymphatic vessels. He illustrated the last with wonderful plates. In 1865 he published a great academic program, "On the Tissue-layers and Spaces of the Body." In this he introduced a new classification which is still in use. He pointed out that all serous spaces arise in the mesoderm and are lined with the special membrane which "His called endothelial." His epic monograph on the embryology of the chick appeared in 1868. During 1880–85 his "Anatomie menschlicher Embryonen," in which the human embryo was studied as a whole, came out.

His was an artist of skill and a photographer of parts. He sought to teach his pupils by means of microphotography, lantern slides, and models. In 1866 he invented a microtome, which led him to the idea of graphic reconstructions of the embryo in two and three dimensions. The His-Steger models, now common in many anatomical museums, are permanent evidence of his success in demonstrating morphological relations in dimensional space.

His founded several societies but no school. His pupils, Franz Keibel and Franklin P. Mall, carried to a conclusion his work on the anatomy of the human embryo.

Wilhelm His died in 1904.

[From Fernelius' Universa Medicina, Geneva, 1679.]

BOOKSHELF BROWSING

THE STORY OF THE DEVELOPMENT OF CHOLECYSTOGRAPHY*

EVARTS A. GRAHAM, M.D.

ST. LOUIS, MO.

WHEN I was asked by Dr. Alvarez to give the first Walter C. Alvarez Lecture before this society on the proposed title of "The Story of the Development of Cholecystography" I felt embarrassed about accepting the invitation. The chief reason for the embarrassment was that I felt that I could hardly discuss this matter frankly without perhaps conveying the idea that I had an exaggerated impression of the importance of cholecystography in comparison with other medical discoveries. Dr. Alvarez, however, was so insistent and advanced such excellent arguments in favor of my presenting an informal account of the various things which led up to the development of cholecystography that I finally consented. My reluctance to accept the invitation was in no way concerned with any lack of appreciation of the high honor which has been accorded to me in being able to be the first to occupy the distinguished position of Alvarez Lecturer. I am one of many who have a very great admiration for the remarkable accomplishments which Dr. Alvarez has achieved in changing our thoughts and ideas about the physiology of the alimentary canal. I am also one of many who have been greatly impressed by the splendid achievements of this society and of its many distinguished members. Accordingly I, a mere surgeon, feel great humility in being selected to stand before this group of men to initiate a long line of lectures which will be given in the future by many of the most prominent men in the medical profession.

Probably the real origin of my interest in cholecystography was a more extensive training in chemistry than was usual for members of the medical profession and especially for a surgeon. With a desire to be able to appreciate better the rapidly developing chemical ideas which were coming into medicine, and with a hope that a better knowledge of chemistry might enable one to advance the science of medicine, I gave up my small surgical practice and spent the years of 1913 and 1914 at the University of Chicago in the study of chemistry. The time so devoted was fruitful to the extent that it enabled me to think somewhat in chemical terms and thus to take advantage of the possibilities of the application of some relatively simple chemistry to the problem of the improved diagnosis of gall-bladder disease.

It is difficult to recall exactly how the idea of the possibility of visualizing the

* First Alvarez Lecture. Read at the 33d Annual Meeting, American Gastro-Enterological Association, Atlantic City, May 5–6, 1930.

gall bladder by the use of phenolphthalein derivatives presented itself. On several occasions a former member, the late Walter Mills, and I had spoken of the desirability of visualizing the gall bladder in some manner comparable to the visualization of the stomach and other parts of the alimentary canal. No satisfactory method, however, suggested itself until suddenly one evening, in the winter of 1922, the idea occurred to me that since Abel and Rowntree had demonstrated the fact that the chlorinated phenolphthaleins are excreted almost entirely through the bile it might be possible, by substituting for the chlorine atoms other atoms which would be opaque to the *x*-ray, to obtain a shadow of the gall bladder.

Acting on this suggestion I began to consult catalogues of various manufacturing chemical firms to see if I could obtain some phenolphthaleins containing bromine or iodine atoms which were already prepared. If I had been unable to obtain any from the manufacturers I intended to attempt the preparation of some of them myself, or to have them made under my direction. However, I was able to obtain some of the free acid of tetraiodophenolphthalein from the Eastman Kodak Co. This was advertised in a list of various indicators. After receiving the material I turned it over to Warren Cole, in July, 1923, and asked him to inject it into some animals to see if he could visualize their gall bladders with it. Dr. Cole had just completed serving his residency in surgery at the Barnes Hospital and had become a member of the department as an assistant in surgery. Before injecting the material into dogs we converted it into the sodium salt because the free acid was naturally less soluble than the sodium salt. Six dogs were injected intravenously, and *x*-ray photographs were made of the gall bladder regions in all of them at frequent intervals after the injection. In five of the dogs no shadow was obtained, but fortunately a faint shadow was obtained in the sixth one. At first we were at a loss to understand why we had obtained a faint shadow in one dog but none at all in the other five animals. The idea then occurred to us that the reason for the failure was probably due to the fact that the animals were not fasting and that, therefore, the injected substance was not staying in the gall bladder for a long enough time to be concentrated and, therefore, to make a shadow. From the standpoint of the future development of cholecystography we often feel grateful to that one dog which cast a shadow, probably because he was accidentally given no food. If we had failed to get a shadow in all of these animals we probably should have abandoned the whole idea as a fruitless one. It is curious on how fragile a thread the destiny of some events hangs. When we came to investigate the matter we found that, as a matter of fact, through some mishap the animal keeper during the time of the experiment had for some reason neglected to feed the one dog on the morning of the injection but he had fed all of the others. Greater efficiency on the part of the animal keeper would doubtless have resulted in a complete failure of our experiment and, therefore, we would have given up the whole idea. Sometimes efficiency can be a curse.

With the clue that the failure to cast a shadow was due to the presence of food in the stomach and duodenum it was then a relatively simple matter to determine that we could obtain shadows in almost every instance in our experimental animals if we were careful to make the injections during a fasting period. Problems of dosage then came up and it was necessary to make a large number of injections in order to determine what would constitute a safe dose for the human being. At about this time Glover H. Copher, another member of the Department of Surgery, was added to the group conducting the investigation. The problem was particularly complicated because of the fact that in several instances our experimental animals died after receiving injections which were considerably

smaller than those which had been given to other animals that survived. There was also present before us the well known fact that organic iodine compounds are in general much more reactive than their bromine homologues. This fact made us turn hopefully to the bromine compound, although of course we could predict that the dose of it required to give a shadow of comparable density would be larger than that required for the iodine compound because of the greater atomic weight of the iodine. Accordingly we enlisted the services of the Mallinckrodt Chemical Works of St. Louis who very generously put at our disposal one of their chemists to make a large number of preparations for us. We were eager to try various bromine and iodine substitution products, not only of phenolphthalein but also of other substances which might have possible advantages. We were also interested in knowing whether a more complete saturation of the phenolphthalein molecule with iodine or bromine such as, for example, an octaiodo compound instead of a tetraiodo compound might have greater advantages because of the much greater amount of iodine contained in the molecule. At all events the Mallinckrodt Chemical Works finally supplied us with an exceptionally pure product of the sodium salt of tetrabromphenolphthalein. We injected this material into animals and found that we got good shadows of the gall bladder with much less toxic effects, in spite of the larger dose required, than we had previously obtained from the use of the tetraiodophenolphthalein which we had obtained. This fact made us feel that for the time being it would be safer to use the bromine compound for human beings than the iodine product.

Up to that time our only idea in visualizing the gall bladder had been to introduce something into it which would visualize any contained stones or deformities of the organ. A colored woman in the Barnes Hospital who presented a very characteristic clinical picture of gallstones seemed to present satisfactory conditions for the first trial in the human. We carefully calculated what the proper dose of the substance would be if injected into her and we gave her the calculated amount of the sodium salt of tetrabromphenolphthalein. I may say that Mills was much interested in the outcome of this first trial on the human of this material and we all had great hopes that we would be able to get a sharp image of gallstones in the woman's gall bladder. An ordinary *x*-ray film before the injection of the dye had failed to show any stones. To our great disappointment and consternation the patient showed no shadow at all of her gall bladder after injection, in spite of a series of films which were made. Our disappointment was made more intense by the fact that I operated upon this patient and found a gall bladder which contained many stones of different sizes. It seemed to us, therefore, for the moment, as if our high hopes of improving the diagnosis of gall-bladder disease had been dashed to the ground. Soon, however, the idea occurred to us that since we had been obtaining excellent shadows in our experimental animals, which presumably had normal gall bladders, the reason for our failure to produce a shadow in a markedly diseased gall bladder might be because the diseased gall bladder could not properly concentrate the material which was brought to it. We also, of course, took into consideration the possibility that in the diseased gall bladder there might have been an obstruction of the cystic duct which prevented the entrance of the material into the organ, but in the case in which we had had a failure I had found an abundance of bile in the gall bladder at the time of operation and also no evidence even suggestive of an obstruction of the cystic duct. We were, therefore, forced to believe that a diseased wall in itself might be sufficient to result in non-visualization because of the failure of concentration. This conclusion seemed to be an obvious one to draw from the work of Rous and McMaster on the con-

centrating function of the normal gall bladder.

This conclusion led us to the next step which was to inject some patients who supposedly had normal gall bladders. We were gratified to obtain well visualized gall bladders in two or three such individuals. This result, while gratifying, made it necessary to change our whole conception of the possible applicability of such a test to the patient. For instead of having a method which would with certainty reveal gallstones in the *x*-ray picture we found that we were, on the contrary, dealing with a method which was more of a functional test of the gall bladder and one which would show the gall bladder most plainly under normal conditions, and not at all in those conditions in which the organ was very badly diseased no matter whether stones were present or not. The recognition of the fact that this new method of visualization of the gall bladder was really a functional test was brought out in most of our early writings on the subject and we were, therefore, amazed to discover how many years were required before there was more or less general recognition of this fact. We have always felt, however, that there were many advantages in being able to test the function of the gall bladder because, after all, symptoms are only an expression of disturbed function. At this time we felt that we were able to predict with some certainty that in order to have a good visualization of the gall bladder certain conditions were necessary. First, the material must get into the blood stream in sufficient amount. Second, it must be excreted by the liver into the bile in sufficient amount. Third, it must get into the gall bladder. Fourth, the gall bladder must be sufficiently normal to be able to concentrate its contents adequately by the absorption of water. If a single link in this chain of events were defective then either faint visualization or non-visualization would occur.

More and more patients presenting different sorts of disturbances of the biliary tract were injected and the results seemed fully to justify our prediction as to what might be expected from this new method of diagnosis. However, we were not entirely satisfied with the material because in concentrations which would give really striking shadows we sometimes had rather severe reactions. We were, therefore, led to continue a search for a more satisfactory substance. We tried the calcium salt of tetrabromphenolphthalein, instead of the sodium salt. During all of this time we were also engaged in the preparation of many other substances which we thought might have theoretical possibilities of visualizing the gall bladder. In the preparation of these substances, some of which had never been made before, we were greatly helped by the generous cooperation of the Mallinckrodt Chemical Works. In all we tried 48 different substances, of which 13 were shown to visualize the gall bladder. These various substances are listed in our book.[1] Most of these 13 substances had disadvantages of one kind or another.

While making the effort to find some more desirable substance chemists were also engaged in attempting to make a much more highly purified product of tetraiodophenolphthalein than had been commercially possible before this time. They succeeded in their effort and because the iodine compound had many advantages over the other substances which were able to visualize the gall bladder, we returned to the use of the sodium salt of tetraiodophenolphthalein. At about this time Whitaker and Milliken[2] published their article which seemed to indicate that tetraiodophenolphthalein had advantages over tetrabromphenolphthalein. In view, however, of our previous experience in being unable to obtain a product of tetraiodo-

[1] Graham, E. A., Cole, Warren H., Copher, Glover H., Moore, Sherwood. Diseases of the Gall Bladder and Bile Ducts. Phila., Lea and Febiger, 1928.

[2] Whitaker, L. R., and Milliken, G. A. Comparison of sodium tetrabromophenolphthalein with sodium tetraiodophenolphthalein in gall bladder radiography. *Surg., Gynec. Obst.*, 40: 17, 1925.

phenolphthalein on the market, which could be confidently assumed to be free from certain impurities which gave rise to toxic effects, and also because Whitaker and Milliken had reported on the use of the material in only one human being, we were unwilling to recommend wholeheartedly a return to the use of tetraiodophenolphthalein for fear that tragedies might occur at the hands of those who might not be familiar with the dangers inherent in an impure product, and who might also be unfamiliar with the difficulties which existed at that time of manufacturing a pure product. For those reasons then we were somewhat slow to recommend for general use a return to tetraiodophenolphthalein. After the manufacture of the tetraiodophenolphthalein had reached such a state that one could count on obtaining a pure product we then directed our attention to the preparation of the isomeric compound which ordinarily goes under the chemical name of phenoltetraiodophthalein. In this compound the four iodine atoms are in a different part of the molecule. Again we were fortunate in being able to obtain a pure preparation and we, therefore, began experiments with the sodium salt of this isomeric compound. We felt that this substance would have the additional advantage in that not only would it visualize the gall bladder in the same way as tetraiodophenolphthalein, but it would also enable one to carry out simultaneously a test of the excretory power of the liver by virtue of the fact that it stained the serum. Our hopes in this respect were fully justified and for several years, therefore, it has been upon this substance which we have relied. Incidentally, we discovered that a slightly smaller dose of this substance is required for visualization than of the tetraiodophenolphthalein. We do not feel that the ideal substance has yet been found and we are still hoping to prepare something which can perhaps be given hypodermically and be free from all toxic effects in the concentrations necessary to use.

The first demonstration of cholecystography before a Medical Society occurred in February, 1924, at the St. Louis meeting of the Congress of Internal Medicine. The first publication on the subject was[1] "Roentgenological Examination of the Gall Bladder. Preliminary Report of a New Method Utilizing the Intravenous Injection of Tetrabromphenolphthalein." The word cholecystography was first employed in the title of one of our papers which appeared in the *Journal of the American Medical Association* on January 3, 1925.

Up to April 15 there had been examined at the Barnes Hospital by cholecystography 3529 patients, of whom 2618 were examined by the intravenous method and 911 by the oral method.

As is well known there have been so many modifications of the method proposed that it has been difficult to become familiar with all of them. Most of these modifications, however, have been discussed in our book on "Diseases of the Gall Bladder and Bile Ducts." It will not be possible for me to refer to them here.

Reference has already been made to the fact that in turning to phenoltetraiodophthalein we hoped to have not only a substance which would visualize the gall bladder but also one which would simultaneously enable us to test the excretory power of the liver, in a manner similar to the Rosenthal method with phenoltetrachlorphthalein. Soon after the beginning of its employment we discovered that patients who had a high retention of the dye were poor risks for operation. We have, therefore, placed a considerable amount of confidence in this method of examining a patient in order to determine his suitability for operation at a particular time. We were able also to find that even when the retention was high and when, therefore, the patient was a bad risk for operation at that time he could become a better risk, with a corresponding reduction in the amount of retention of the dye,

[1] *J. A. M. A.*, Feb. 23, 1924.

by keeping him at rest in bed, by the administration of an abundant amount of carbohydrate, preferably in the form of glucose, a little calcium and generous amounts of fluid. Almost invariably a patient who was a poor risk, simply because of his damaged liver, could be made a good risk for operation by our resorting to the plan of treatment outlined here. The effect, both of the test in guiding us as to operative risk and the plan of preparing patients already mentioned, has had a noticeable result in reducing our operative mortality. For example, during the last three years since we have used phenoltetraiodophthalein for the purpose mentioned, our mortality in the operation of cholecystectomy has been only 0.4 per cent. The mortality in the preceding three years was 6.0 per cent. In other words, our present mortality is only a small fraction of what it was before we began to place some reliance on the excretion of phenoltetraiodophthalein as a means of gauging the operability of a patient.

In addition to the invaluable help given to the working out of the problem of cholecystography by Cole and Copher, the splendid assistance and many suggestions furnished by Dr. Sherwood Moore, the director of the Roentgenological Department of the hospital, and by Dr. Joseph W. Larimore, a member of the association, were of the greatest possible assistance; in fact it would hardly have been possible for us three surgeons to have been able to work out this problem entirely alone. Not only were the matters of the *x*-ray technique worked out by Dr. Moore and his associates but also many other valuable suggestions were obtained from both him and Dr. Larimore. It has always been a matter of great personal regret to me that the untimely death of Walter Mills, at the very beginning of the application of cholecystography to the human, prevented his eager and enthusiastic cooperation in the development of the problem.

Finally, I should like to add a few words of appreciation of the kindly and charitable support with which the various members of your organization have received cholecystography as a method of diagnosis. It is seldom that one finds a new procedure taken up so charitably and so enthusiastically as was the reception accorded this particular method by the various members of your organization. For this charitable reception the author now wishes to give his sincere thanks.

BOOK REVIEWS

PATHOLOGIE UND KLINIK IN EINZELDARSTELLUNGEN. By L. Aschoff, H. Elias, H. Eppinger, C. Sternberg and K. F. Wenckebach. Band I DER APPENDICITISCHE ANFALL SEINE ATIOLOGIE UND PATHOGENESE. By Ludwig Aschoff. Mit einem kurzen beitrag über die lymphgefassverhaltnisse am menschlichen wurmfortsatz. By Dr. H. Seng. 127 pp., 36 illus., Berlin, Julius Springer, 1930.

This is the first of a new series of modern monographs. Aschoff's study of the appendix from the pathological point of view is based on thousands of cases and, like everything written by the Dean of present-day pathology, will be found extremely interesting.

A TEXTBOOK OF SURGERY. By John Homans, M.D. Springfield, Ill., Charles C. Thomas, 1931.

In the preface one reads, "The aim of this book, for which Dr. Harvey Cushing supplied the inspiration, is to record and amplify lectures now given by members of the surgical department of the Harvard Medical School. These lectures . . . are intended to teach the fundamentals and something of the practice of surgery." It fulfils this promise.

Although the contents vary with each contributor the book as a whole is very compact and even. Some of the lectures are monographs on the subject discussed, and in some instances have been published before.

The following men have written chapters: Arthur W. Allen, David Cheever, Edward D. Churchill, Harvey Cushing, William P. Graves, Robert B. Greenough, John Homans, Gilbert Horrax, Daniel F. Jones, William E. Ladd, George A. Leland, Howard A. Lothrop, Richard H. Miller, Edward H. Nichols, Robert B. Osgood, Charles A Porter, Tracy J. Putnam, Lyman G. Richards, Edward P. Richardson, Channing C. Simmons, J. Herbert Waite, Wyman Whittemore, and Philip D. Wilson.

There is a special bibliographical index and the illustrations are by Willard C. Shepard.

It is a book that has a place in the surgical literature of the day. It covers the surgical field in a satisfying manner and one instantly senses he is reading honest, conservative, solid, and time-tried but modern opinions. It is a work that well might be in any surgeon's library.

TECHNIQUE AND RESULTS OF GRAFTING SKIN. By H. Kenrick Christie M.S. (N. Z.) F.R.C.S. (Eng.) 64 p., London, H. K. Lewis & Co. Ltd., 1930.

This little book on the technique of skin grafting is a splendid resume of the subject. It is based on a series of 30 cases of ulcers of the extremities, including all the types that are to be found with the object of devising a standard method of operative cure for such cases. As all of these cases were traced for two or three years afterwards, the results are of exceptional interest.

THE CONWAY LETTERS. The Correspondence of Anne, Viscountess Conway, Henry More and their Friends, 1642–1684. By Marjorie Hope Nicolson. New Haven, Yale Univ. Press, 1931.

These letters are delightful to all those interested in history and they have a special interest to physicians on account of the concrete picture that they give of the patient of that day.

Anne Finch, Viscountess of Conway, had a fever at the age of twelve which was felt to be responsible for the severe headaches which she had for the rest of her life. A brilliant woman, interested in the study of languages, philosophy, mathematics, religion and every form of culture, she came in contact with all of the great men of the day.

She was treated by William Harvey, Sir Theodore Turquet de Mayerne, Lake and Thomas Ridgely and her brother, John Finch. In her letters will be found the complete story of the attempts made to relieve her condition, which was little understood.

These letters are a distinct contribution to the cultural and medical history of England in the seventeenth century and both Miss Nicolson and the Yale University Press should be congratulated on making them up in such splendid form.

SURGICAL OPERATIONS. By Sir Frederick Treves, Bart. G.C.V.O., C.B., LL.D., F.R.C.S., and Cecil P. G. Wakeley, F.R.C.S. Eng.,

F.R.S. Edin. Ed. 5, 535 pp. N. Y., Paul B. Hoeber, Inc., 1931.

This thoroughly tried and reliable classic has been revised and brought up to date by Dr. Wakeley and may be highly recommended for the purpose for which it is intended—a rapid and authoritative insight into surgical operations for the student. Even the experienced surgeon will find this book worthwhile to have at hand for rapid reference.

Die Mund-und Halsoperationen. By Prof. Dr. J. Soerensen. 457 pp. Berlin, Urban & Schwarzenberg, 1930.

Prof. Soerensen of Berlin has produced an unusually well-illustrated book on "Operations of the Mouth and Neck." Forty-eight colored plates render this in actuality a splendid atlas on the subject.

It is to be regretted that in a large octavo of almost 500 text pages there is no index, though the table of contents is quite detailed. The bibliography that we have come to expect in German works is also missing though references are quite frequent throughout the book.

Lehrbuch Der Mund Und Kieferchirurgie. By Prof. Dr. Erich Sonntag and Prof. Dr. Wolfgang Rosenthal. 444 pp. Leipsig, Georg Thieme, 1930.

This modern text of mouth and jaw surgery is intended for physicians, dentists and students. Concise and up-to-date, it is splendidly illustrated with 501 halftones. The chapter on "Malformation and Deformity" is worthy of special mention as is that on "Tumors," whereas it is to be regretted that only 30 pages are devoted to "Injuries."

Jahrbuch Für Röntgenologen, 1930. Under the editorial supervision of O. Rigler-Hufeland. 220 p. Berlin, Walter De Gruyter & Co., 1931.

The year's progress in roentgenology for 1930 is presented in this concise form, written under the editorial supervision of O. Rigler-Hufeland, Brummer, Burgheim, Chantraine, Dyroff, Grebe, Hedfeld, Hin, Kaestle, Kohlmann, Peltason, St. Rothman, A. Seyerlein, F. Schmitz, J. Schutze, M. Schwarz, W. Stock, O. Strauss, W. Teschendorf, K. Weber, and R. Werner. The authors present in this publication a review of the journal literature in roentgenology, not only summarized but criticized, this criticism making the summary all the more valuable.

The articles referred to are grouped under: "Physics, Roentgen Ray Biology, Technique, Diagnosis, Therapy, Roentgen Ray Damages and Treatment, Radium Therapy." The reviews are well done and a fair amount of credit is given to American authors, who are usually rather scantily referred to in such German reviews. Indeed, the number of references to American literature is really gratifying as compared with past experiences. Every radiologist who reads German should find in this work a great deal of convenient material for ready reference.

James T. Case.

Practical Radiation Therapy. By Ira I. Kaplan, B.S., M.D. With a special chapter on Applied X-ray Physics, by Carl B. Braestrup, B.Sc., P.E. 354 p., 227 illus. Phila., W. B. Saunders Co., 1931.

There has been a long-felt need for a work in English giving just the information supplied by Dr. Kaplan's book. Several excellent publications on this subject have appeared in foreign languages, and some in English on radium therapy, but nothing in English of a recent nature which deals in practical terms and in such an understandable and generally satisfactory manner with the problems of practical *x*-ray and radium therapy. In most books of this sort, the preliminary chapters, sometimes amounting to a very considerable portion of the work, deal with apparatus and are accompanied by numerous photographs of equipment of almost every make in order to avoid hurting the feelings of individual apparatus manufacturers. In this book we find the pages devoted to this kind of literature reduced to a minimum. The entire subject of history, definition and action of *x*-rays and radium and the production of *x*-rays and radium and radium emanation are all taken care of in 40 pages, leaving the remaining 350 pages for the practical discussion of the clinical aspects. Illustrations are freely employed in a manner to be commended.

All the way through one wonders what were the final results in the cases in which the "before and after" illustrations are presented. It would be interesting to have an additional note on each case as to the remote result. One's feeling about the value of radiation therapy

would be considerably improved if more data as to the outcome were given.

It seems that stress has been laid upon the use of radium rather than *x*-rays. Combination of both *x*-rays and radium is recommended in suitable instances. The author evidently accepts the teachings of Regaud, who prefers a very long application of a relatively small amount of radiation in the treatment of most malignancies, when the radiant source is near the lesion.

There are chapters on endothermy, including the description of apparatus and indications; the nursing care of patients suffering from malignant conditions; the plan and scope of a unit radiation therapy plant in a general hospital; and a brief discussion of electrical accidents and radiation burns.

The final page, giving a list of references for collateral reading, indicates the author's recognition of the book's shortcoming; namely, that it is too brief and too elementary in some of its discussions. On the whole, however, this work fills a long-awaited and much needed gap in American radiological literature.

James T. Case.

Modern Surgery. By John Chalmers DaCosta, M.D., LL.D., F.A.C.S. Assisted by Benjamin Lipshutz, M.D., F.A.C.S., 1404 pp. Ed. 10, Phila. W. B. Saunders Co., 1931.

The tenth edition of DaCosta's "Modern Surgery" brings up-to-date a favorite work of American surgeons.

Dr. DaCosta points out in his Preface that "In the present edition we have taken the course of revising the different sections ourselves instead of having them looked to by friends and associates." The section by Dr. Chevalier Jackson on "Direct Laryngoscopy, Bronchoscopy, Esophagoscopy and Gastroscopy" still remains. The section on *x*-ray has been omitted as the author feels that this subject has grown to such a point that it should be treated in a separate volume.

As was to be expected from the pen of this illustrious surgeon, the work presents a splendid picture of the surgery of today. That some things are included and others omitted, which another author would have put in, is to be expected in a work of this character. Dr. DaCosta makes the point in his Preface that the matter of inclusion or omission is entirely up to the author and that the author of a book of this kind must particularly "try to avoid being caught in the subtle trap of fashion in surgery." This the author has ably avoided and DaCosta's "Modern Surgery," in its tenth edition, may be accepted as a reliable guide to the surgery of today.

Cancer. International contributions to the study of cancer in honor of James Ewing. By Frank E. Adair, M.D., F.A.C.S., 480 pages, Phila., J. B. Lippincott Co., 1931.

This book, published in honor of Dr. Ewing's sixty-fourth birthday, consists of as fine a resume of the subject of cancer from all angles as is available today between any book covers. With contributions from the leading specialists in cancer from all parts of the world, it may be considered the outstanding work on the subject today.

Preceding the foreword of the book is an appreciation of Dr. Ewing by William H. Welch which sums up the achievements of Dr. Ewing as only Dr. Welch could do. Dr. Ewing needs no volume to establish his place as the outstanding authority on cancer today, but the fact that he has inspired such a volume may be added to his credit as another achievement of no mean import.

William Henry Welch at Eighty. A memorial record of celebrations around the world in his honor. Edited by Victor O. Freeburg. 230 pp. Milbank Memorial Fund, 1930.

This is one of the most beautifully published volumes of this kind that has yet appeared and is a worthwhile memento of the memorable celebrations of Dr. Welch's birthday.

It is stated that this book is one of a limited edition of 500 copies printed for presentation. It is indeed a book that any collector would be proud to own.

It contains not only the account of the celebrations in Baltimore and Washington but an account of celebrations around the world together with 14 illustrations, most of them reproductions of testimonials to Dr. Welch.

Text-book of Pathology. By Dr. E. T. Bell. 627 pp. Phila., Lea & Febiger, 1930.

This new "Text-Book of Pathology" makes

a particular appeal on account of its brevity. There are 627 pages with over 300 illustrations, covering the entire present-day course of study. Particular mention should be made of the splendid plates accompanying the excellent chapter by Prof. Hal Downey of Minneapolis on "Diseases of the Blood."

THE TREATMENT OF CHRONIC DEAFNESS BY THE ELECTROPHONOIDE METHOD OF ZUNDBURGUET. By George C. Cathcart, M.A., M.D. 111 pp. Ed. 2. Humphrey Milford, Oxford Univ. Press, 1931.

The second edition comes to us with the following enthusiastic send-off by the author in his Preface: "I am of opinion from my own experience that until some better form of treatment is invented or discovered no aural specialist can consider himself fully equipped to undertake the treatment of chronic deafness unless he has a Zund-Burguet electrophone." Dr. Cathcart's standing in the otological world is such that his opinion is entitled to more than mere "consideration." The fact that otologists are by no means all of one mind on this subject is indicated by the author's quotations from reviews which criticize other books for recommending this method. The reviewer hesitates to express his own opinion on the subject matter but ventures to say that the book is so well written and presents its case so well that it is entitled to a hearing by otologists so that they may form their own opinion as to the value of the method.

SURGERY. By Francis T. Stewart, M.D. and Walter Estell Lee, M.D., Ed. 6, 1307 pp. Phila., P. Blakiston's Son & Co., Inc., 1931.

This sixth edition of the well-known Stewart and Lee's "A Manual of Surgery" has been brought up-to-date by Dr. Lee. The author has had the advantage of having many chapters gone over by specialists so that proper selection and evaluation of the "new" in surgery has been made. The author's hope "that this revision will be found to be conservative, safe and sound" will be found to have been fulfilled.

BIBLIOTHEQUE DU CANCER. CANCER DU PANCRIA. By H. Hartman & L. Berard, Directeurs, Dr. A. Chalier Secretaire. 330 pp. Paris, Gaston Doin & Cie., 1931.

This is the latest volume of the "Bibliotheque Du Cancer" edited by professors Ch. Oberling & M. Guerin. A 330 page monograph on Cancer of the Pancreas will of course be of interest to the specialist. The subject is thoroughly treated and well illustrated. There is a bibliography of over 30 pages. There is also a table of contents but no index.

PYE'S SURGICAL HANDICRAFT. By H. W. Carson, F.R.C.S. Ed. 10, 641 pp. N. Y., William Wood & Co., 1931.

The tenth edition of the revision of Pye's "Surgical Handicraft" was put into the able hands of Dr. W. H. Carson, who died before the completion of the work. However, as indicated in the publisher's preface, he lived to see every page of the MS. leaving only the Preface to be written.

Many of the older surgeons will remember Pye's Manual from their college days. Revised by Carson, the book is today as practical as ever.

DIE CHIRURGIE DES KROPFES. By Karl Urban. 85pp., Leipzig, Franz Deuticke, 1931.

In a monograph of 85 pages the author presents his technique on goiter operations, based on over thirty years' experience, and over 4000 cases. A work based on such experience always makes interesting reading, even though American surgeons will not be inclined to agree with all the methods of the author. There are over 40 splendid illustrations in this small volume.

CANCER AND SCIENTIFIC RESEARCH. By Barbara Holmes, PH.D. (Cantab.), 158 pp. London, Sheldon Press, 1931.

A short and interesting elementry treatise of 158 pages. It is not intended for the cancer specialist or trained physician. To the beginning student and scientifically inclined layman, the book will furnish an excellent introduction to the subject. It is one of the volumes published in the series "Sheldon Books of Popular Science."

DIE CHIRURGIE DES VEGATIVEN NERVENSYSTEMS. By Erich Hesse. Moscow, Staatsverlag, 1930.

This book is published in Moscow and Leningrad by "Staatsverlag," presumably, therefore, by the Soviet Government.

It is unfortunate that the paper used in the text is transparent and, therefore, makes difficult reading. The colored prints, on the other hand, are printed on special paper, as inserts, leaving little to be desired. The binding is poor.

The subject is one of the utmost importance. The Preface is dated August, 1929, so that allowance must be made for the non-inclusion of material published since then. The breadth of the author's reading is evidenced by the large number of American and English citations in the literature. Thirty references to the writings of Adson give evidence of the careful literary research of the author. His own experience extends, according to his own statement, to over 100 operations on the nervous system. No attention is paid to the technique of operation.

The author emphasizes the fact that the subject covered by this book is new ground for the surgeon and that the apparently established ideas of today may be discarded tomorrow. His own claim is that, at the time of publication, his book represents a fair resume of the status of the subject and a rather careful analysis of the contents confirms this claim.

The neuro surgeon will need this book. The surgeon, who only occasionally sees cases of this character, will be glad to refer to it as occasion offers. The book is a very definite indication that our Russian confreres are very much alive to what is going on elsewhere and it is to be hoped that they will publish more books of this character in order to let the world know what they are doing.

This monograph makes no particular contribution to the advancement of science, but, perhaps, presents the best review obtainable of the present status of the subject and this in itself may be considered a distinct contribution.

Die Knochenbruche und Ihre Behandlung. By Prof. Dr. Hermann Matti. 938 pp. Berlin, Julius Springer, 1931.

In 938 pages with 1000 illustrations, Matti succeeds in presenting the subject of "Fractures and their Treatment" completely and yet without verbosity. Surgeons will find little to criticize in the presentation. As indicated by the extensive bibliography at the end of each chapter, the author knows his literature, and the text indicates a very practical application of this knowledge.

In these days of controversy and discussion of methods and technique of fracture treatment, it is well to have at hand so informative a treatise of the present status of the subject.

Die Gesamte Wiederherstellungs Chirurgie. By Erich Lexer. 1336 pp. Leipzig, J. A. Barth, 1931.

Based largely on experiences in the war, Professor Eric Lexer has revised his surgery into two large well-illustrated volumes, covering the subject thoroughly and completely.

To specialists in this field, the volumes will be indispensable. To every surgeon, reading German, the work will be valuable for reference. The book has over 1900 splendid illustrations and the author has a happy faculty of saying a lot in a few words and of making his subject entertaining as well as scientifically accurate.

Handbuch der Praktischen Chirurgie. By A. Brunner, St. Gallen; W. Felix, Berlin; R. Haecher, Augsburg; A. Herrmannsdorfer, Berlin; R. Nissen, Berlin; F. Sauerbruch, Berlin, G. Schmidt, Munchen. Stuttgart, Ferdinand Enke, 1931.

The second half of Volume II of this splendid set is quite on a par with the previous volumes of the series which were reviewed in the January, 1930 issue of this Journal. It completes what, in the opinion of the reviewer, is the outstanding handbook of practical surgery in any language today.

Lateral Curvature of the Spine and Round Shoulders. By Robert W. Lovett, M.D., Sc.D. Ed. 5, 240 pp. Phila., P. Blakiston's Son & Co., Inc., 1931.

It is a splendid thing to have Dr. Lovett's classic revised and brought up to date by his former associates. As to the changes in this edition, the editors point out in the Preface that "There has been added Galeazzi's method of treating lateral curvature, a detailed description of the turnbuckle jacket and turnbuckle shell treatment, with reference to the literature and a brief discussion of operative treatment as an adjunct to other methods. The portion of the book devoted to exercises has been practically rewritten, and we wish to express our thanks to Miss W. G. Wright for her assistance in formulating the exercises. Many new illustrations have been added."

With these additions, this book is sure to retain the position it has so long held. It is the best book in the English language on lateral curvature of the spine.

ROENTGEN INTERPRETATION. By George W. Holmes, M.D. and Howard E. Ruggles, M.D. Ed. 4, 326 pp. Phila., Lea & Febiger, 1931.

That this book has gone through four editions is in itself proof of its value. The present volume has been brought thoroughly up-to-date. It is intended as an outline of the most modern methods in the interpretation of *x*-ray films. As the authors say "Such a survey can do little more than cover the essentials of the subject; more detailed text-books, monographs and literature may be relied upon to supply further data, if required." The authors have succeeded in doing what they set out to do with unusual success. The illustrations have been well selected and well reproduced.

In short this is a book that belongs in the library of every man who is doing any work in *x*-ray interpretation.

RADIOLOGISCHE PRAKTIKA. XII and XIII. NORMALE ANATOMIE DES KOPFES IM RÖNTGENBILD (Normal Anatomy of the Head as Seen by the *X*-ray). By Karl Goldhammer. Leipzig, Georg Thieme, 1931.

In the two volumes of this beautiful work we find 74 contact prints in the negative, half of them from the dried skeleton, the other half from the living individual, illustrating all the useful positions for the examination of the skull, facial bones, jaws, and the teeth. In each instance there is a copy of the roentgenogram made from the dried skull, with an outline drawing clearly indicating the exact position in which the exposure was made. Following this there is a similar roentgenogram made on the living patient. Each of the roentgenograms is accompanied by a transparent sheet with lines and carefully numbered references to all the important anatomical structures. The references are in four languages, German, English, French, and Spanish, so that the books should have a very wide sale. The roentgenograms are extremely well done, showing a wealth of detail not ordinarily seen and indeed not capable of reproduction except in the actual photographic prints which make up the books.

Full credit is given to such splendid workers as Holzknecht, Schüller, Mayer, Grashey, and Belot-Lepennetier for their various atlases of the head. The work permits a careful analysis of head roentgenograms, thus allowing its application by experts with long experience and by the less experienced younger colleagues. The dedication reads "To the young physicians as a guide, to the older experienced ones as an advisor."

JAMES T. CASE.

FUNDAMENTAL PRINCIPLES OF ALVEOLODENTAL RADIOLOGY. By Joseph A. Pollia, M.D. Brooklyn, Dental Items of Interest Publ. Company, Inc. 1931.

One often encounters divergence of opinion between dentists and medical radiologists in the interpretation of alveolodental pathology. In the present work, the author, a physician, seems to have adequately met the requirements of dentists, as is attested by the fact that the book is published by a dental organization. The author very properly calls attention to the fact that there is a difference between a clinically satisfactory roentgenogram and the so-called "gallery" roentgenogram. The first of these is characterized by a softness which is due to the grayness of the general tone. The wealth of detail shown in these films is due to the large scale of gradations of the *x*-ray absorption thereon recorded. On the other hand, the "gallery" roentgenogram is for exhibition purposes and appeals from the pictorial rather than from the anatomical aspect. Considerable space is devoted to the discussion of the nature and production of *x*-rays, a fault of most clinical books on radiology. For more than 500 pages the author goes on in encyclopedic detail regarding the technique of dental roentgenography; an analysis of the various pathological processes which increase or diminish radiopacity. The various pathological variations in the index of increased or decreased density and their interpretation consume the rest of the work.

JAMES T. CASE.

RADIOLOGISCHE PRAKTIKA. Band XV. DIE NORMALE ENTWICKLUND DES KNOCHENSYSTEMS IM RÖNTGENBILD (The Normal Development of the Bones as Seen Roent-

genically). By Dr. E. Ruckensteiner. 63 text illus. 11 curves and 3 tables. Leipzig, Georg Thieme, 1931.

This little work of 78 pages ought to be in the hands of every physician who undertakes to do *x*-ray interpretation. Really one cannot make satisfactory interpretations of the roentgenograms of the incompletely developed individual without a knowledge of the rate of ossification of the various centers. In addition there are a number of anomalies of development, with which one ought to be familiar.

All this information is here given in condensed, easily accessible form, and well classified for ready reference. The illustrations consist of both diagrams and roentgenograms, and are freely interspersed. Three excellent tables are appended at the end of the book showing graphically the development of the various epiphyseal centers and the rate of ossification from the first month of fetal life to the age of twenty-four years. These are suitable for framing and displaying upon the walls of consulting or class rooms.

James T. Case.

Technica Radiodiagnostica (Radiodiagnostic Technic). By Prof. Mario Ponzio. 350 text figs. and 96 half-tone inserts. Unione Tipografico Editrice Torinese, 1930.

In this work of a trifle over 400 pages the author has managed to concentrate a large amount of radiodiagnostic information. After the usual introductory chapters on apparatus, one finds a very satisfactory section on dark room technique. The remaining two-thirds of the book is devoted to technical considerations and interpretations. The number of illustrations is naturally limited by the size of the book. For those who read Italian the book will afford a great deal of up-to-date information. There are discussions on the use of lipiodol in otolaryngological, obstetrical, gynecological, and neurological practice, as well as an adequate chapter on the various methods of opaque visualization of the bronchi, gall bladder, and urinary tract.

James T. Case.

Cinchona Tercentenary Celebration and Exhibition at the Wellcome Historical Medical Museum. By Henry S. Wellcome, LL.D., F.S.A., Director, and L. W. G. Malcolm, M.SC. (Cantab.)., F.R.S.E., Conservator. 115 pp., 6 illus., London, The Wellcome Foundation, Ltd., 1930.

Here is another production of the Wellcome Historical Medical Museum with a most interesting list of the exhibits at the Tercentenary Celebration and Exhibition in London.

PRINCIPLES OF PREOPERATIVE & POSTOPERATIVE TREATMENT

BY

REGINALD A. CUTTING, M.A.,PH.D.,M.D.,C.M.

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PRINCIPLES OF PREOPERATIVE & POSTOPERATIVE TREATMENT

Chapter VII

DISTURBANCES OF ACID-BASE EQUILIBRIUM: ACIDOSIS AND ALKALOSIS

The clinical entities comprehended by the terms "acidosis" and its antithesis, "alkalosis," are conditions which, though frequently discussed and actively treated, are often poorly understood and even less well managed. In order clearly to understand these two conditions, it is first necessary to consider at some length the modern physico-chemical theory of acids and bases.

1. Simple Solution, Dissociation, Ions, and pH

Though the class of substances known as acids is a relatively familiar one, even to the laity, the scientific definition of this class of substances has always been a matter of some difficulty. The older definitions, which simply described certain of the properties of acids, such as the turning of blue litmus paper red, causing a sour taste in the mouth, and reacting with alkalis to form salts, were always recognized as being inadequate in that such descriptions were not really definitive at all; not all of the acids fulfil these requirements, whereas other substances, not acids, frequently do fulfil them. As the result of the efforts of physicists and chemists, working in collaboration, it is now possible to formulate a much more satisfactory definition based primarily upon the behavior of acids and alkalis toward the electric current.

As has been appreciated for many years, acids, alkalis, and most salts when in solution in water possess the property of transmitting the current of electricity; other substances when in solution do not possess this property. The first

class of substances are known as "electrolytes," whereas the second are called "non-electrolytes." The difference between these two classes of substances, according to modern concepts,

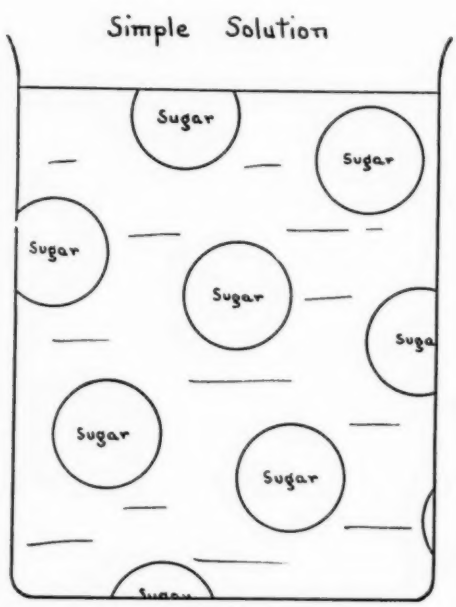


FIG. 36.

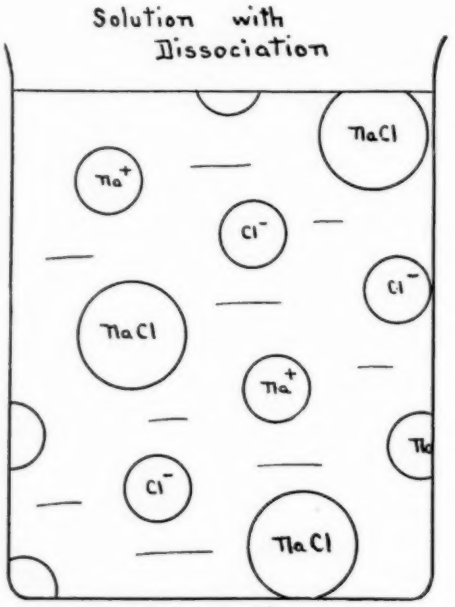


FIG. 37.

is the difference between simple solution and solution with dissociation.

A substance like cane sugar, which goes into simple solution in water, is a non-electrolyte. It dissolves without dissociating, which means that when brought into contact with water it disperses the molecules of which it is composed in such a way that each molecule is equally spaced from every contiguous molecule, the intervening spaces being filled with molecules of water (Fig. 36). The strength of such a solution depends upon the proportion between the number of molecules of the substance dissolved and the number of molecules of the substance in which it is dissolved; a concentrated solution of sugar in water is one in which the sugar molecules are separated by a relatively larger number of water molecules. A

simple solution is a molecular solution, and because molecules possess no electrical properties, such a solution is indifferent to the electrical current.

Substances which not only dissolve but also dissociate, in addition to passing into solution in the previously described manner, proceed one step further in that a certain number of the molecules of the substance dissolved undergo still further cleavage and disintegrate into particles known as ions (Fig. 37). Ions may be simple, consisting of a single element, such as hydrogen or chlorine; or they may be more complex, consisting of two elements, such as a hydroxyl radical (OH); or they may be still more complex, consisting of a number of elements combined, e.g., acid carbonate (HCO_3). These ionic particles are not merely chemical elements or simple combinations of elements, but differ by virtue of the fact that they carry charges of electricity upon them. Certain of these particles or ions possess positive charges of electricity, whereas others possess negative charges.

This property of ions, viz., the carrying of charges of electricity upon them, is expressed graphically by affixing to the chemical symbol of the ion a plus or minus sign according to the nature of the charge of electricity carried. Particles of hydrogen and certain other radicals which break off from molecules to form ions carry positive charges of electricity upon them, and substances which carry charges of positive electricity upon them are known as cations, whereas the radical OH and certain other radicals when they break off from a molecule to form ions carry a negative charge of electricity upon them and are known as anions.

To recapitulate, an ionic solution is a solution of a substance which not only disintegrates to form molecules which are equally spaced one from the other, but which also further disintegrates with respect to a certain number of molecules into smaller particles, or ions, which carry upon them electric charges, some of the charges being positive and some of them negative.

The mechanism of the passage of a current through an ionic solution need not be described here, except to state that it involves a migration of ions and a discharge of the electric charges carried upon them.

Neither ions nor molecules are stationary in space. The molecules of a substance in solution are continually in motion, one molecule bombarding against another and being repelled, only to rebound upon still another. Indeed, it is this continual bombardment which keeps the molecules equally spaced. In this sense even a simple solution may be considered as unstable.

An ionic solution, however, is unstable in another sense, in that the molecules of which it is composed are continually disintegrating into ions and subsequently recombining again to form molecules. This reaction takes place in a definite way, so that for a given strength of solution, and for a given substance, there is at any moment a definite proportion between the number of intact molecules and the number of molecules which have become dissociated into ions. It follows that the amount of dissociation of a substance, and, therefore, its ability to conduct electricity is always constant for given amounts of substances in given solution. Pure water, which is a combination of hydrogen with hydroxyl radicals is a very poor conductor of electricity, which is equivalent to saying that only a very small number of its molecules dissociate to form ions.

Without our going into the methods of determining the figures quoted, it has been calculated that a liter of water contains 1/10,000,000 of a gram of hydrogen in ionic form. A "normal" solution of hydrogen, by definition, contains 1 gm. of ionized hydrogen to the liter. Consequently distilled water has a normalcy of 1/10,000,000, which fact is expressed mathematically in terms of hydrogen ion concentration, as the normality, or N, multiplied by 10 to the minus seven power. Because *N multiplied by* 10 *to the minus* 7 *power* is an unwieldy and inconvenient expression, Sorensen has suggested

the use of a condensed expression which, mathematically, is the *logarithm of the reciprocal of the hydrogen ion concentration*, or in chemical shorthand the pH; pH as here and subsequently described covers only a relatively narrow band of values in the acid-base scale on either side of neutrality; it is inapplicable as a measure of strong acidities or strong basicities, since these represent values beyond the pH scale. Distilled water, according to this terminology, is said to have a pH of 7.

The concentration of hydroxyl ions in distilled water has likewise been determined, and it has been found that the hydroxyl ion concentration is precisely the same as the hydrogen ion concentration (Fig. 38).

This property is a general property of neutral solutions, i.e., in neutral solutions precisely the same number of hydroxyl ions as hydrogen ions occur. In distilled water, therefore, the hydrogen ion concentration, expressed as pH, is 7, and the hydroxyl ion concentration, expressed similarly, is also 7.

The fact has already been stated that in any given solution and at any given moment the number of molecules which have become dissociated as ions bear to the number of molecules not so ionized a constant relationship, and this fact may be expressed mathematically by saying that the concentration of hydrogen ions multiplied by the concentration of hydroxyl ions in any solution is always a constant. This constant is expressed for distilled water by adding the exponents of the figures already given, that is, the concentration of hydrogen ions being "10 to the minus 7 power" (10^{-7}), and the concentration of the hydroxyl ions being also "10 to the minus 7 power" (10^{-7}), the dissociation constant for distilled water is "10 to the minus 14 power" (10^{-14}).

II. The Relation of Hydrogen Ions to Acidity

When certain dissociable substances are dissolved in water the relationship of the hydrogen ion concentration to the hydroxyl ion concentration is not as one is to one. Acids in

solution contain a preponderance of hydrogen ions. This can be illustrated concretely by considering what happens when hydrochloric acid is added to distilled water. Distilled water

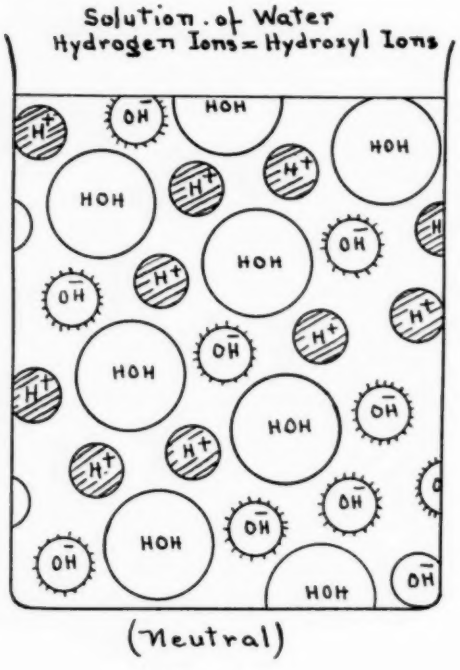


FIG. 38.

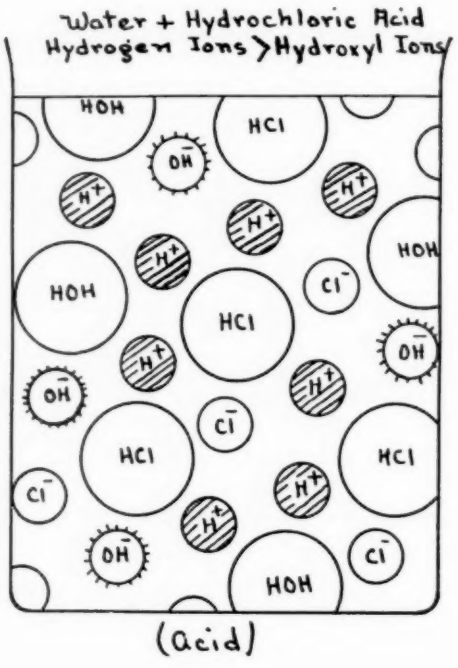


FIG. 39.

is neutral, i.e., it contains in solution the same number of hydrogen ions as hydroxyl ions and, being only slightly dissociated, contains only a small number of hydrogen and hydroxyl ions. Hydrochloric acid, when it goes into solution, dissociates to a relatively much larger extent; it has a high "dissociation constant," only a few hydrochloric acid molecules being found in the solution as such, and a correspondingly larger number of hydrochloric acid molecules being dissociated into hydrogen ions and chlorine ions. In other words, the solution, water, which formerly contained a relatively small number of hydrogen ions and hydroxyl ions, becomes, because of the addition of hydrochloric acid, tremendously augmented by hydrogen ions derived from the dissociation of the hydrochloric acid, whereas, on the other hand, the chlorine ions,

which are liberated from the hydrochloric acid molecules during the dissociation of hydrochloric acid, being chlorine ions and not hydroxyl ions, augment the hydroxyl ion concentration not at all.

Such a solution, which contains a preponderance of hydrogen ions over hydroxyl ions, possesses the property of acidity, and, accordingly, substances which dissociate to form a preponderance of hydrogen ions are known as acids (Fig. 39).

In an acid solution, however, the general law that the product of the number of hydrogen ions and hydroxyl ions is a constant (that is, 10 to the minus 14 power) still holds good. For this reason, if the hydrogen ion concentration of a solution is known, the hydroxyl ion concentration can be computed by a simple process of mathematics, viz., by substracting from 14 the number used to designate the pH. Furthermore, the pH being expressed in terms not of a number but of the reciprocal of a number, higher concentrations of hydrogen ions are expressed by smaller numbers, viz., a solution having a pH of 6 has a greater acidity than a solution having a pH of 7, and likewise a solution having a pH of 5 is still more strongly acid than a solution having a pH of 6.

It should be remembered also that since the Sorensen method of expressing pH deals with logarithmic values, a pH value of 6 represents just 10 times as many hydrogen ions as a pH value of 7, whereas a solution having a pH value of 5 contains 10 times 10, or 100, times as many hydrogen ions as a solution with a pH of 7.

This constitutes a rather hasty résumé of what happens when acids and bases are allowed to go into solution in water and the theory of hydrogen ion concentration.

III. Buffers and Buffer Action

Although the addition of an acid to a watery solution always changes the latter in the direction of increased acidity or decreased alkalinity, as the case may be, there are certain solutions of substances to which acids or bases may be added

without changing appreciably the hydrogen ion concentration. Such solutions are known as buffer solutions, and since the fluids of the body are essentially buffer solutions, it becomes necessary to understand the phenomenon of buffering as well as the phenomena of simple solution and dissociation which have already been described.

Buffer action can best be understood by considering a specific example: The acid known as acetic acid, $CH_3.COOH$, ionizes in solution to a relatively small extent; it has a low dissociation constant. The sodium salt of acetic acid, sodium acetate, on the other hand, dissociates to a relatively great extent; it has a high dissociation constant. If, now, these two substances be added to distilled water, such a solution will contain, because of the dissociation characteristics of these substances, a relatively large number of acetic acid molecules and a relatively small number of sodium acetate molecules, together with a certain number of ions representing the disintegration of the rest of the acetic acid molecules and sodium acetate molecules. A relatively small number of hydrogen ions results, because acetic acid dissociates only to a small degree, as already stated. A relatively larger number of sodium ions occurs in solution because sodium acetate dissociates to a relatively high degree. A relatively still larger number of acetate ions results because acetate ions are formed by the disintegration of both acetic acid and sodium acetate.

If hydrochloric acid be added now to such a mixture, hydrochloric acid being an acid which dissociates to a very large extent, there immediately results the addition of a few hydrochloric acid molecules but a correspondingly larger number of hydrogen and chlorine ions. There now exist in solution the following ions: hydrogen, chlorine, sodium, and acetate. It has already been stated that acetic acid dissociates in watery solution to only a limited extent, which, considered in another way, means that hydrogen ions and acetate ions can exist together in the same solution to only a limited extent. Since this is true, the addition of hydrogen ions, as the result

of the addition of hydrochloric acid to the solution, simply results in effecting a readjustment of the constituent parts of the solution whereby the hydrogen ions liberated by the hydrochlo-

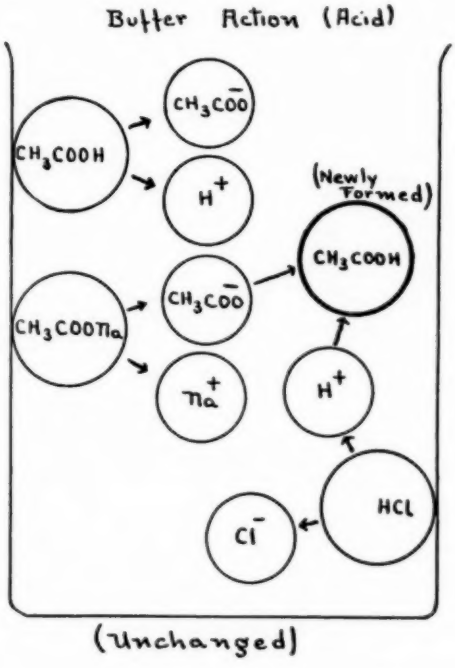


FIG. 40.

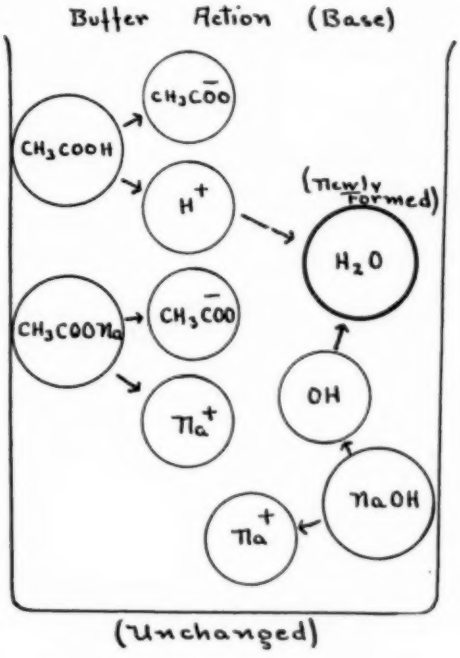


FIG. 41.

ric acid immediately recombine with a corresponding number of acetate ions, derived mostly from the sodium acetate, to re-form acetic acid in the molecular form. Since, furthermore, acetic acid in molecular form in solution has no acidic properties, the hydrogen ion concentration of the solution remains virtually as it was before (Fig. 40).

A similar readjustment without change in pH results when sodium hydroxide is added to a solution of acetic acid and sodium acetate. In this case, as the result of the solution of sodium hydroxide, a large number of hydroxyl ions are immediately liberated. Water, however, is only slightly dissociable, i.e., it is possible for only a few hydrogen and hydroxyl ions to exist together in the same watery solution. Accordingly, the hydroxyl ions derived from the dissociation of the sodium

hydroxide immediately combine with the hydrogen ions already present in the solution to form water. This leaves opportunity for more hydrogen ions to be split off in the solution, and previously undissociated acetic acid, therefore, dissociates to form hydrogen ions and acetic ions, with the net result that the hydrogen ion concentration under these conditions again readjusts itself to the same level as it was before (Fig. 41).

The fact that only a small number of hydrogen ions and of hydroxyl ions can exist in a watery solution at the same time explains why considerable quantities of water may be added to properly buffered solutions without changing the number of hydrogen and hydroxyl ions appreciably, i.e., without changing the pH value. Certain buffered solutions may be diluted with water as much as a thousand times without appreciably changing their pH values.

In general it may be stated that salts of weak acids and weak bases usually exert a buffer action, and since the blood stream and the various tissue fluids contain relatively considerable quantities of such salts, it will be readily appreciated that in the biological sciences buffer action assumes great importance.

IV. Human Blood Considered as a Buffer Solution

Normal human blood is slightly alkaline in reaction; the pH value may be given as from 7.3 to 7.5, individual bloods varying in health between these narrow limits. The blood serum is approximately 0.2 of a pH higher than that of whole blood, and the pH of the other body fluids probably very closely approximates and follows any changes in the pH value of the blood plasma.

As long as the pH value of the blood and the various tissue fluids is not seriously disturbed life is not in danger by reason of acid-base imbalance. Variations to the acid side are tolerated to a slight degree, a pH of 7.0 for a short time being apparently not inconsistent with life, though figures much below this

invariably are accompanied by dissolution. A pH of 7.0 is considered as the point below which coma occurs. On the alkaline side variations beyond 7.8 are incompatible with life, and as long as life lasts are accompanied by tetany, so that the extreme range of blood reaction compatible with life lies approximately between a pH of 7.0 and a pH of 7.8.

The conditions of acidosis and alkalosis are not always accompanied by an actual change in the pH value of blood. They usually represent, rather, changes in the reserve capacity of the blood to withstand the addition of acids of alkalis without corresponding changes in hydrogen ion concentration, and accordingly represent assaults upon the normal buffer capacity of the blood.

A. Compensated and Uncompensated Acidosis and Alkalosis: The principal buffer in the blood is sodium bicarbonate, a salt of the weak acid, carbonic acid. Carbonic acid exists dissolved in the water of the blood stream, and being a weak acid it dissociates but slightly. Sodium bicarbonate, a salt of sodium with carbonic acid, dissociates to a relatively great extent. There are in the blood stream at all times (a) hydrogen and hydroxyl ions derived from the dissociation of water, (b) sodium, and acid-carbonate ions derived from the dissociation of sodium bicarbonate, and (c) hydrogen and carbonate ions derived from the dissociation of carbonic acid. Since acid-carbonate is an acid radical and further dissociates into hydrogen ions and carbonate ions, there is, then, in the blood stream at all times an equilibrium between hydrogen, hydroxyl, sodium, and carbonate ions. If to such a solution some acid be added, for example, HX, a certain number of hydrogen ions are thereby added to the solution, plus a corresponding number of X ions.

A readjustment of equilibrium now takes place in accordance with which the hydrogen ions liberated by the acid HX unite with the hydroxyl ions derived from the dissociation of water to form new molecules of water. Since the product of the concentrations of hydrogen and hydroxyl ions in a

watery solution is always constant and small, a corresponding number of hydrogen ions are immediately released by the dissociation of carbonic acid, with the result that equilibrium is reestablished almost precisely as before, and the pH of the solution remains unchanged.

It must be appreciated, however, that there is a limit to the amount of acid which can be added to a buffered solution without actually changing its pH. The amount of acid which may be added to blood as the result of this buffer action without changing its acidity is known as the "acid reserve" of the blood, and varies with the amount of acid already accommodated.

It should be apparent from these considerations that the addition of acid to a buffered solution, such as blood, which condition may now be given the name "acidosis," may occur up to a certain point without changing the actual pH of such a solution. Such an acidosis is known as a "compensated acidosis." On the other hand, if acids be added to such a solution in excess of the capacity of the buffer action of that solution an actual change in the pH results, and the condition is then known as an "uncompensated acidosis." It should also be remarked that in a solution such as blood which normally has an alkaline reaction, i.e., which has an excess of hydroxyl ions over the number of hydrogen ions, acidosis, whether compensated or uncompensated, represents a relative value, that is, not usually an absolute acidity of the blood, but rather a diminished alkalinity.

Bicarbonates are by no means the only buffer substances upon which the animal body depends for acid-base stability. All the salts of weak acids, contained both within the blood cells and dissolved in the plasma, are capable of performing a similar function. Among the best known of these are the phosphates and the alkali salts of the proteins, which latter behave like weak acids and include reduced hemoglobin and oxyhemoglobin. The primary cleavage products of proteins also apparently exhibit the same property to a minor degree, the

proteoses and peptones. The blood is thus supplied with not one, but several, protective buffer mechanisms all of which must be disturbed before actual changes in hydrogen ion concentration can take place to any measurable degree.

The bicarbonates, however, represent the most sensitive buffer properties of all these substances, an action which must be overcome or at least gravely disturbed before inroads are made upon the reserve capacity of the others. This fact has been epitomized by Henderson in his designation of the bicarbonates as the "first line of defense" of the body against acidosis and alkalosis.

B. THE PRACTICAL MEASUREMENT OF ACIDOSIS AND ALKALOSIS, PLASMA CO_2 COMBINING POWER: Although for certain scientific and experimental purposes it is highly desirable to have some means of determining the hydrogen ion concentration of blood, from a clinical standpoint such determinations are of relatively little value, for by the time either acidosis or alkalosis has advanced to the point of seriously changing the normal hydrogen ion concentration of the blood of a patient that patient is in immediate danger of dissolution, and nothing that can be done for him will be likely to be of much avail. The changes of importance clinically are those which involve the reduction or reinforcement of the buffer action of the blood and which, therefore, represent compensated acidosis or alkalosis, i.e., the early morbid changes in the direction of uncompensated acidosis or alkalosis. Fortunately these changes are capable of determination with a fair degree of accuracy by quantitative chemical methods, and, provided that adequate laboratory facilities be at hand, the clinician need never be in doubt as to the status of the acid-base balance of his patient.

The principle underlying the most practical and usual determination of acid-base balance is the measurement of the so-called "carbon dioxide combining power of the blood." To understand the meaning of this term it is necessary to know that there normally exists in the blood stream sufficient free

carbonic acid to combine with all the alkalis present and not already bound by stronger acids. This means that the excess alkali of the blood exists in the form of bicarbonates. In other words, the alkali radicals of the blood primarily react with the stronger acids to form relatively stable salts, i.e., carbonates, and secondarily with carbonic acid, of which there is always an excess in the blood stream, to form bicarbonates which latter, being salts of a weak acid, are relatively unstable.

The manner in which the bicarbonates act in the presence of the addition of stronger acids to a solution has already been discussed at length as constituting a typical buffer action, and it is evident from this description that the measure of the amount of bicarbonates in such a solution is the measure of the amount of acid which could be added to the solution before the actual reaction of the latter would begin to change.

The most sensitive measure of the milder forms of acidosis and alkalosis might thus well consist, then, in measuring the percentage of bicarbonates in the blood. Chemically this would be a relatively difficult undertaking and from a practical point of view the inaccuracy at best would be considerable. It is, however, much easier to measure the bicarbonate content indirectly by determining the amount of carbon dioxide gas which can be displaced from a unit volume of blood by some acid which possesses the property of splitting CO_2 from bicarbonates, but not from carbonates, and this is the method which has been found best adapted to clinical needs.

Practically, the method consists, according to the method of Van Slyke,[1] in (a) the withdrawal of a small amount of blood by venepuncture into a tube containing a suitable anticoagulant; (b) the separation of the plasma from the cells of this blood by centrifugalization and the saturation of the resulting plasma with CO_2 at the normal CO_2 tension of alveolar air; (c) the addition of lactic acid to a unit quantity of the plasma; (d) the collection and measurement of the volume of CO_2 gas liberated thereby; and (e) the computation in cubic centimeters of the amount of the gas which would have been liberated had

100 c.c. of blood plasma been used under standard conditions of temperature and atmospheric pressure. Since the volume of gas liberated from 100 c.c. is actually a percentage relationship, volumes of CO_2 per 100 c.c. of blood plasma, the Co_2 combining power is expressed in terms of "volumes per cent."

The normal values determined on the basis of many estimations of this variable have been established as from 53 to 77 c.c. of carbon dioxide gas to 100 c.c. of blood plasma. The variable itself is called the "plasma-carbon-dioxide-combining-power." The fact that the chemical process of determining this variable involves the dissociation of the gas rather than the combining of it with some other substance should not mislead one, since combination and dissociation are reversible reactions, and although the practical chemical analysis involves dissociation, the process in the body, the reaction of clinical interest, is the process of combination.

Obviously, from these considerations, the CO_2 combining power of the blood is reduced when an excess of hydrogen ions is present in the blood stream; these hydrogen ions existing not as free hydrogen ions but combined in stable compounds as carbonate salts, the more carbonate found in this manner the less carbonate there is to combine with carbonic acid in the form of bicarbonate; consequently the less the CO_2 combining power, and the more severe the acidosis. Conversely the fewer the hydrogen ions in the blood stream, the more the bicarbonate; consequently, the higher the carbon dioxide combining power, and the less the acidosis, or in exaggerated cases the greater is the alkalosis.

Carbon dioxide combining powers in excess of 77 or thereabouts are considered as indicating clinical alkalosis; carbon dioxide combining powers less than 53 are considered as indicating clinical acidosis.

To recapitulate, acidosis and alkalosis represent a condition in which the normal buffer action of the blood is diminished or, in the severe cases, is actually overcome. In moderate acidosis and alkalosis there is merely a reduction in the reserve capacity

of the blood to withstand the further addition of hydrogen ions and hydroxyl ions respectively without at the same time changing the hydrogen ion concentration. In severe acidosis and alkalosis the reserve capacity becomes actually or substantially nil, and the further addition of hydrogen and hydroxyl ions has a direct effect in actually changing the hydrogen ion concentration. Furthermore, whereas the buffer action of blood is dependent upon its content of several salts of weak acids, the buffer salt which bears the brunt of the burden is the salt of carbonic acid, bicarbonate. The entire subject of acidosis and alkalosis is, therefore, closely connected with the chemical reactions of bicarbonates or, since bicarbonates are salts of carbonic acid, with the chemical reactions of carbonic acid, or, again, since carbonic acid represents hydrated carbon dioxide, with carbon dioxide.

c. The Respiratory Regulation of the Carbonic-acid-base-bicarbonate Ratio: All metabolic processes are very closely associated with the production of carbon dioxide, since proteins, carbohydrates, and fats all contain the two constituents of carbon dioxide, carbon and oxygen, and the complete catabolism of proteins, carbohydrates, and fats invariably yields the two elements not as such, but in combination as carbon dioxide gas. Carbon dioxide gas, however, in the presence of water not only goes into physical solution in the water with readiness, but also rather actively combines chemically with it to form the weak acid, carbonic acid.

Carbonic acid, however, being an acid, tends to react with any basic radicals that may be present in a solution to form bicarbonates. The principal base-forming radicals present in blood are sodium and potassium. Consequently, the principal bicarbonates are compounds of sodium and potassium with the bicarbonate ion. The sodium and potassium bicarbonates may be termed collectively the "base bicarbonates."

Since the production of carbonic acid is so fundamental a process in metabolism it is not surprising to find that the body has developed a very special and complex mechanism for

dealing with and ridding itself of this particular acid, for it is obvious that if such were not the case no purely palliative device for maintaining a stable acid-base balance could long remain effective. The principal mechanism evolved to subserve this function constitutes one-half of the cycle known as respiration.

1. *Internal and External Respiration:* The alveolar epithelium of the lungs has long been recognized as the tissue particularly responsible for the elimination of carbon dioxide from the body; this function it subserves in conjunction with a process of absorption of oxygen, both processes together representing the phenomenon known as *external respiration.*

External respiration, however, alone constitutes but a part of the total respiratory process. Fundamentally, respiration is a function of every individual cell of which the body is composed; carbon dioxide must be eliminated and oxygen must be absorbed from each cell in order that the cellular biochemical processes known as life may continue. This cellular exchange of oxygen and carbon dioxide is known as *internal respiration.*

The blood, both cells and plasma, constitutes the medium by which the processes of internal and external respiration are maintained and correlated; it, by virtue of its motility, reduplicates both peripherally in the lungs and centrally at the individual cell a process of oxygen liberation and carbon dioxide absorption. The absorption, transportation, and elimination of carbon dioxide in respiration represents the fundamental biochemical device for the regulation of carbon dioxide, carbonic acid, and the salts of carbonic acid.

Carbon dioxide gas, when liberated from the individual cell by diffusion through the cell membrane, comes first in contact not actually with any of the cells of the blood stream, but with plasma, or, in most cases, with that modification of plasma which is called lymph and which circulates slowly through the various tissue spaces between individual cells.

Carbon dioxide when liberated into a watery medium like the plasma or lymph can assume four physico-chemical

forms: (1) it can exist in simple physical solution as CO_2, (2) it can combine with water to form carbonic acid according to the formula $CO_2 + H_2O \rightarrow H_2CO_3$, (3) it can react with dissolved bases to form carbonates according to the formula $H_2CO_3 + 2NaOH \rightarrow Na_2CO_3 + 2H_2O$ and (4) as carbonic acid it can react with carbonates to form bicarbonates according to the reaction $Na_2CO_3 + H_2CO_3 \rightarrow 2NaHCO_3$.

Although a certain rather small percentage of the carbon dioxide formed by the metabolism of the body is capable of being transported by the plasma in simple solution (12 per cent according to Doisy, Briggs, Eaton, and Chambers[2] under the conditions present at the time when arterial blood is changing to venous blood) a greater part is carried by the buffers (25.3 per cent), and a still greater part is carried by the agency of the hemoglobin of the erythrocytes (53.5 per cent).

Simple solution of carbon dioxide in water and reaction with water to form carbonic acid would constitute entirely inadequate mechanisms for purposes of carbon dioxide transportation and would speedily result in local cellular death because of regional acidosis. The buffer action of base bicarbonates dissolved in the plasma or lymph immediately comes to the rescue in an ionic readjustment which not only avoids any appreciable change in acidity, in accordance with the general principles previously outlined, but which at the same time considerably augments the carrying capacity of the medium for carbon dioxide by virtue of the fact that as soon as a readjustment to any moderate given quantity of carbonic acid has been made the addition of still more carbonic acid simply results in a repetition of the adjustment. This buffer action of *plasma and lymph bicarbonates* is ordinarily amply adequate for purposes of hydrogen ion stablilization and carbon dioxide transportation *locally* and for *relatively small collections of tissue cells.*

A considerable part of the function of the lymph and plasma buffers is, however, merely intermediary; they serve to a considerable extent in the capacity of vehicles to bridge the

gap between the fixed cells of the tissues and the specialized gas transporting cells of the circulation, the erythrocytes. The carbon dioxide carrying capacity of the ultimate carbon dioxide carrier, the circulating blood, is very much augmented by its erythrocyte content. The erythrocyte is as dependent upon buffer action for its capacity to mobilize carbon dioxide as is lymph or plasma, and the principal buffer is the same, base bicarbonate.

Proteins, of which hemoglobin is an example, characteristically behave as weak acids. As is well known, the protein, hemoglobin, is capable of existing in two normal forms, reduced hemoglobin and oxyhemoglobin. These two forms of hemoglobin differ in their respective dissociation constants, which is merely a technical way of expressing the fact that they present different acidity values; oxyhemoglobin is a stronger acid than reduced hemoglobin. Now since erythrocytes contain bicarbonates as well as hemoglobin, the relation between the bicarbonates existing as such and the bicarbonates existing in chemical combination with hemoglobin in the erythrocyte depends upon the chemical state in which the hemoglobin exists, whether reduced or oxygenated. In the oxygenated state hemoglobin chemically binds relatively large quantities of base bicarbonates, but when reduction of hemoglobin occurs base bicarbonates are liberated, due to the fact that the acidity of the hemoglobin is diminished. This reversible reaction accounts for a considerable part of the mechanism of respiration.

When the erythrocytes, coming from the pulmonary circulation, approach the individual cells of which the body is composed, swept on by the impulsion of the heart beat, they contain relatively large amounts of oxyhemoglobin because of their previous circuit through the lungs; a relatively large amount of the base bicarbonates contained within them is, therefore, chemically bound as bicarbonates of oxyhemoglobin. Oxygen, however, being in very loose combination with the hemoglobin begins to diffuse out through the cell membrane as

soon as the partial pressure of this gas in the surrounding plasma becomes low. As soon as reduction of the hemoglobin occurs, however, its acidity is decreased, and base bicarbonate is released. This bicarbonate, furthermore, becomes immediately available for chemical combination with acids and accordingly allows diffusion into the erythrocyte of a quantity of the carbonic acid previously transported by the extracellular plasma.

The exact reverse of this process constitutes the fundamental mechanism involved in external respiration. As soon as the carbon-dioxide-laden erythrocyte is returned to the pulmonary circulation, it finds itself in a medium in which the partial pressure of oxygen on the outside of the cell membrane is greater than the partial pressure within; reduced hemoglobin, having a marked affinity for oxygen, rapidly becomes oxidized, but during this process it becomes much more strongly acid due to the formation of oxyhemoglobin. Its acidic properties immediately express themselves by a chemical reaction with base bicarbonate by which the latter becomes bound. The base bicarbonate, however, no longer existing as such, is unable to take care of its previous quotum of carbon dioxide, which, therefore, immediately diffuses out through the limiting membrane of the erythrocyte and is discharged as gas into the alveolar air and so through the bronchi and trachea into the external atmosphere.

Acidosis and alkalosis are thus seen to depend primarily upon the ratio in the blood between carbonic acid and base bicarbonate and this ratio depends primarily, in turn, upon the process of respiration. The balance in the blood between carbonic acid content and base bicarbonate content is very delicate and is maintained in health at a value of about 1 part carbonic acid to 20 parts of base bicarbonate.

This value is not, of course, an arbitrary one but depends upon a long chain of balanced reactions starting with the partial pressure of carbon dioxide in the alveolar air of the lungs. It determines the ratio between the realtive amounts

of carbonic acid and base bicarbonate in the erythrocytes, which in turn determines the ratio between the amounts of carbonic acid and base bicarbonate in the plasma, which finally, in turn, fundamentally determines the acid and alkali reserve capacity of the plasma.

v. The Specific Factors Producing Acidosis and Alkalosis

As has been previously shown, the acid-base balance depends directly upon the carbonic-acid-base-bicarbonate ratio. Since, moreover, both of the factors concerned in this ratio, carbonic acid and base bicarbonate, are capable of undergoing an increase or a decrease with respect to the other to produce a condition of unstable equilibrium, four fundamental derangements of acid-base balance are possible, two of which represent a condition of acidosis, and two a condition of alkalosis. This situation is represented by the following schema:

Acidosis results from (1) an increase in carbonic acid or (2) a decrease in base bicarbonate.

Alkalosis results from (1) a decrease in carbonic acid or (2) an increase in base bicarbonate.

It remains to consider these four variations somewhat in detail.

a. Acidosis Resulting from Excess of Carbon Dioxide (Carbonic Acid): The acidosis resulting from retention of excess amounts of carbonic acid is essentially a respiratory acidosis, since the formation of carbonic acid and the carbon dioxide content of the blood stand in a reciprocal relation, the one with the other, and the carbon dioxide content of the blood is a direct function of the efficiency of the respiratory mechanism. Since, however, respiration depends not only upon the external respiratory movements and the partial pressure of gases within the respiratory tract but also upon the *circulation*, retention of carbon dioxide within the blood stream may result from either external respiratory or circulatory embarrassment.

Respiratory acidosis may therefore be expected to occur in:

(1) Conditions of venous stasis such as are encountered in cardiac decompensation,

(2) Conditions in which there is a depression of the respiratory center, e.g., in various toxemias and morphine narcosis,

(3) Conditions in which the inspired air contains unduly high percentages of carbon dioxide,

(4) Conditions in which considerable areas of the respiratory epithelium of the lungs become incapacitated, e.g., pulmonary atelectasis, pneumonia, and many other respiratory diseases, and

(5) Conditions in which the hemoglobin content of the erythrocytes is disturbed, e.g., anemia and carbon monoxide poisoning.

Mild degrees of acidosis can rather easily be demonstrated to follow the voluntary holding of the breath. Under these circumstances external respiration largely fails, and because it fails internal respiration is depressed, and carbon dioxide accumulates rapidly. Carbonic acid derived from the accumulating carbon dioxide tends to exhaust the reserve buffer action of the base bicarbonates, and a condition of compensated acidosis tends to develop. The extent to which such a voluntary acidosis can be made to progress is strictly limited, however, because of a stimulatory reflex action on the respiratory center by the carbon dioxide contained in the blood stream; the respiratory center is very sensitive to local changes in acidity, and when disturbed in this manner promptly enforces a compensatory hyperpnea.

Under abnormal conditions, however, a condition of disturbed respiratory function can easily be induced which cannot be overcome by even the most vigorous hyperpnea. In pneumonia, massive collapse of the lung, drowning, impaction of foreign bodies, such as diphtheritic membranes in the trachea, and similar mechanical conditions, no amount of hyperpnea may avail, the interchange of gases previously described as external respiration being physically impossible.

Circulatory embarrassment tends to produce acidosis by interference both with internal and external respiration The movement of the erythrocytes may be so sluggish that the respiratory mechanism completely breaks down, and compensated acidosis followed by uncompensated acidosis and death speedily ensues.

The treatment of this variety of acidosis should be sufficiently obvious from a consideration of its pathogenesis and need not be elaborated at this point. The fundamental objects of treatment are (1) the restitution of a normal circulation, (2) the supplying of an adequate amount of oxygen to the respiratory epithelium of the lungs, and (3) reinforcement of the hemoglobin content of the blood stream, as by blood transfusion.

Plans of treatment involving an attack upon the acid base balance, as such, would, of course, be relatively futile.

B. Acidosis Resulting from Decreases in Base Bicarbonates: A discussion of the variety of acidosis characterized by decreases in the base bicarbonate of the blood stream involves a number of digressions. There are several different ways in which the base bicarbonate may be reduced, the mechanisms of which are sufficiently important to merit separate discussion. A simple schema, like the following, will serve to introduce the fundamental reactions.

Decreases in base bicarbonate result in general either (1) from excessive elimination of base bicarbonate from the body or (2) from replacement of the bicarbonate ion of the base bicarbonate with some other ion to form a new compound. These two factors together with their variations are represented thus:

1. Elimination of base bicarbonate by way of:
   a. The alimentary tract
   b. The kidney
2. Replacement of the bicarbonate ion by:
   a. The lactate ion
   b. The chlorine ion

c. The acid-phosphate and acid-sulphate ions

d. The diacetate and beta-oxybutyrate ions

1. *Elimination of Base Bicarbonate by Way of the Gastrointestinal Tract:* Considerable quantities of alkaline secretion are poured into the gastrointestinal tract daily (1) by way of the bile ducts from the liver, (2) by way of the pancreatic duct from the pancreas, and (3) directly into the intestinal lumen through the intrinsic secretory action of the intestinal glands. Much of the alkalinity of all of these secretions is dependent upon their base bicarbonate content. Normally this base bicarbonate is not lost to the body but goes through a cycle of secretion and reabsorption; however, under certain abnormal conditions, like severe diarrhea, much of the absorptive power of the intestine may be lost, and the bowel movements may then represent relatively unchanged alkaline intestinal juices. The loss of base bicarbonate under these circumstances may be relatively great.

2. *Elimination of Base Bicarbonate by Way of the Urinary Tract:* A certain amount of base bicarbonate is secreted by the kidney in the urine. The amount ordinarily is not great unless considerable base bicarbonate has been just previously ingested. The kidney, however, assumes an essential part of the function of maintaining the normal base bicarbonate level in the blood stream, and since any normal function is likely to undergo perversion, depletion of the normal base bicarbonate becomes a real or potential danger whenever the secretory action of the kidney becomes deranged in the direction of the establishment of polyuria. Clinically this mechanism is probably of relatively little importance except when it is associated with other complicating mechanisms.

3. *Acidosis Due to Replacement in the Blood Stream of Base Bicarbonate Ions by Other More Reactive Ions:* The mechanism of acidosis which depends upon replacement in the blood stream of base bicarbonate ions with other ions of more reactive properties is one which frequently assumes alarming proportions clinically. So true is this in connection with one group of ions

derived from certain ketone bodies in the disease diabetes that in the minds of some otherwise fairly well informed practitioners of medicine acidosis is invariably interpreted as this particular form of acidosis, i.e., diabetic acidosis or "ketosis." Actually, however, diabetic acidosis represents but one of a number of sub-classes of disturbance of acid base equilibrium characterized by the same fundamental reaction, the replacement of base bicarbonate with acid radicals.

a. Acidosis Due to Excessive Production of Lactate Ions: Lactic acid is produced from the glycogen of muscle tissue during the process of muscular contraction; the normal lactic acid content of resting muscle (about 0.015 per cent) may be increased ten or more times by repeated muscular stimulation.[3]

In the absence of free oxygen this process of lactic acid formation occurs *pari passu* with glycogen decrease, and may be continued by a process of stimulation only up to a certain maximal point since eventually the developing acidity checks further conversion of glycogen to lactic acid. In the presence of free oxygen, however, a certain part of the lactic acid (probably about 20 per cent) is oxidized to carbon dioxide and water, and the energy derived from this reaction is believed to be instrumental in reconverting the remainder of the lactic acid to glycogen during periods of muscular rest.

The concentration of lactic acid in actively contracting muscular tissue is thus seen to be dependent upon two factors (1) the amount of activity, and (2) the presence or absence of oxygen.

Lactic acid, when formed in considerable amounts, as during strenuous exercise, finds its way directly into the blood stream and may increase the normal lactic acid concentration of the blood by as many as ten times. Because of the reactions of the blood previously described it must be evident, however, that free acid cannot exist in the circulation as such; it immediately combines with the most available alkalis to form salts. The most available alkalis are the base bicarbonates, especially sodium bicarbonate, so that within the circulation lactic acid

exists almost solely as sodium lactate. During the process of formation of this sodium lactate, moreover, a certain amount of the available base carbonates is evidently rendered no longer available. Under these circumstances a condition of acidosis ensues, the gravity of which is dependent upon the amount of lactic acid poured into the circulation. There is, of course, in the lungs no mechanism for ridding the body of excesses of sodium lactate; the kidney assumes this function.

Since, moreover, the kidney serves as the organ of excretion for lactic acid the concentration of this substance in the blood is not only dependent upon the amount of its formation in muscular tissue but also upon the excretory efficiency of the kidney. Lactic acid acidosis, therefore, tends to become maximal (1) during strenuous muscular efforts, (2) in the absence of normal oxygenation, i.e., when the respiratory or circulatory function is embarrassed, and (3) when the kidney is damaged. Clinically lactic acid acidosis occurs in its severest forms in connection with convulsions, especially in the presence of the hypoxidation due to failure of the circulation and retention due to kidney damage.

b. Acidosis Due to Excess of Chlorine Ions: The biological reactions and functions of the chlorine ion are not by any means completely understood. It is well known, however, that the concentration of chlorine ions in the blood stream is normally maintained at a relatively constant level regardless of the intake of chlorine-containing compounds by mouth. This regulatory function is subserved chiefly by the kidneys, and when these organs undergo degenerative changes the chlorine ion concentration of the blood tends to increase, unless the chloride intake is at the same time commensurately diminished. The chlorine ion displaces the bicarbonate ion from base forming radicals and therefore is capable of producing a chlorine acidosis.

Chlorine acidosis may result either (1) from excessive chloride administration, whether in the form of hydrochloric acid, sodium chloride, calcium chloride or ammonium chloride,

or (2) from chloride retention, whether the retention be due to actual kidney damage or to the anuria of blood concentration.

c. Acidosis Due to Excess of Acid Phosphate or Acid Sulphate Ions: The kidneys perform an important, though secondary, function in maintaining the acid-base balance of the body. As is well known, the urine becomes acid or alkaline in accordance very largely with the reaction of food material absorbed from the gastrointestinal tract. Though normally more or less acid in reaction, the urine may readily be rendered temporarily basic by the ingestion of alkaline substances and also may be very quickly changed back again by the feeding of acids.

The normal acidity of the urine reflects its primary function in acid-base control, the elimination of non-volatile acids. Within the blood stream the stronger acids react with the buffer salts, mainly the phosphates, and are excreted chiefly as acid phosphates. Weak acids may be excreted as such. Bases are excreted by the kidney not as free alkalis but mainly as disodium phosphate and sodium bicarbonate.

When considerable quantities of strong acids require excretion an interesting protective phenomenon is displayed by the kidney. Were all the acid to be excreted as acid phosphates a serious drain would rather evidently be brought to bear on the concentration of the latter in the blood. The phosphates, being important buffer substance, could not well be spared for the purpose. To meet the emergency the kidney assumes the function of ammonia formation and thereby provides a method of neutralization in accordance with which acids are excreted as ammonium salts, thus sparing the important phosphates for purposes of buffer action.

Kidney damage results in retention of acid phosphates and sulphates; these two radicals react with the bicarbonates and decrease the alkali reserve capacity in the typical manner.

d. Acidosis Due to Excess Diacetate and Beta-Oxybutyrate Ions-Ketosis: "Ketosis" may be defined as a condition in which an excess of ketone bodies occurs in the blood

stream, and a consequent appearance of such bodies occurs in the urine.

The phenomenon of ketosis has been recognized for many years as occurring in connection with a number of diverse conditions: (1) starvation, whether voluntarily induced or secondary to obstructive carinoma of the stomach, stricture of the esophagus and kindred conditions; (2) after ether and chloroform anesthesia; (3) in connection with parturition, (4) as an accompaniment of various febrile conditions, especially the exanthemata in children, and (5) *par excellence* in diabetes mellitus.

Formerly, the origin of the so-called ketone bodies which appear in the urine in ketosis, beta-hydroxybutyric acid, acetoacetic acid, and acetone (by the presence of which the condition was primarily recognized clinically), and the fundamental metabolic changes underlying the development of the condition were not understood. At present one is in a better position to understand these changes, and although certain features of the disorder are not satisfactorily solved the fundamental aspects of the condition are now fairly well appreciated.

The line of reasoning formerly promulgated to account for the appearance of the acetone or ketone bodies in the urine was that during the process of starvation, in diabetes, or in whatever other connection ketosis might occur, there was an abnormal and compensatory metabolism of the body proteins, a mechanism which was invoked by the organism whenever there was a deficiency of, or an abnormal demand for, sugar; in this process sugar was believed to be formed from protein. At present it is well established that the ketone bodies are produced not in connection with a process of metamorphosis of protein to sugar (a process which is entirely possible, to be sure), but in connection rather with an incomplete combustion of fats. Such incomplete combustion occurs for some reason not well understood whenever there is an inadequate oxidation of sugar, a phenomenon which has been popularly expressed by saying that the fats "burn in the flame of the carbohy-

drates," and the ketone bodies represent the "smoke" which results from imperfect combustion.

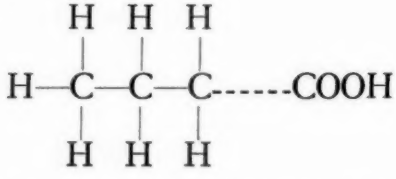
In order to understand the precise manner of production of the ketone bodies one must be familiar with the metabolism of fats. The process of fat metabolism may be reviewed profitably by a consideration of the metabolism of the patient's own stored fats during a period of starvation. It is well known that during starvation the more available sources of energy are invaded first, and that the carbohydrates constitute the first line of defense. The dextrose circulating in the blood stream is first metabolized, and this process rapidly depletes the concentration of sugar in the circulation. A compensatory mechanism is, however, contemporaneouly brought into play to maintain the blood sugar concentration by virtue of which additional dextrose is released from the tissues rich in dextrose, especially the muscles and the liver, and coincidentally additional dextrose is released by a process of cleavage from stored glycogen (polymerized dextrose). Ultimately the store of glycogen, however, is so reduced that the metabolism of dextrose is no longer capable of maintaining the normal energy requirements of the organism. Under these circumstances the second most available source of energy is invaded, viz., the fats.

Stored fats occur in the body in the natural fat reservoirs, in the subcutaneous connective tissues, in the retroperitoneal tissues, and certain of the organs such as the liver, in the neutral form, i.e., as esters of the fatty acids with glycerol. Three molecules of fatty acid combine with one molecule of glycerol to form one molecule of neutral fat.

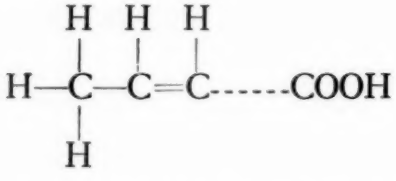
The first process in the catabolism of fat both in vitro, and probably also in vivo, consists in the splitting of the fatty acid radical from the molecule of glycerol. The further catabolism of the glycerol molecule is irrelevant to the production of ketosis and consequently will not be considered.

The oxidation of the fatty acids, however, represents the essential catabolism of the fats, and it is during the process of cleavage of these substances that the ketone bodies are formed.

The fatty acids are relatively simple combinations of carbon, hydrogen, and oxygen, though the molecules at the outset are comparatively large. The molecule consists of a long aliphatic or straight chain, in the case of the saturated series of fatty acids, thus:



In the case of the unsaturated series the structure is the same except for the occurrence of a "double bond" somewhere in the series of carbon atoms, thus:



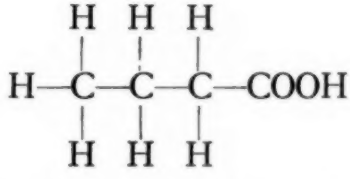
The fatty acids characteristically entering into the metabolism of the human body are mainly three, stearic, palmitic, and oleic, of which the first two are saturated and the last unsaturated.

Obviously, because of the composition of the fatty acid molecule, the end-products of metabolic processes must be carbon dioxide and water, and these are the products evolved when catabolism is complete, i.e., when the complete toll of energy has been abstracted from the fatty acid molecule.

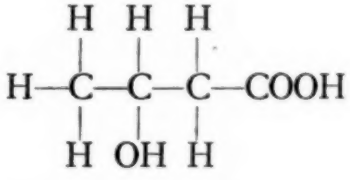
The process by which the intermediate products are formed is unfortunately more or less speculative, due, more than likely, to the transitory character of the reactions involved, according to which the concentration of any given one of the intermediate products at any particular moment is insufficient, normally, to permit of its isolation and identification by chemical means.

All of the usual fatty acid molecules consist of an even number of carbon atoms; palmitic acid consists of 16 carbon atoms, and stearic and oleic acids each have 18.

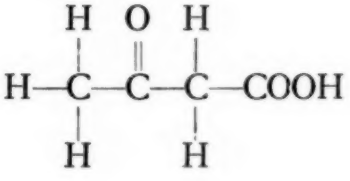
On the basis of certain experimental work with animals Knoop,[4] in 1904, promulgated the hypothesis that oxidation of the fatty acids always occurs at the "beta" carbon atom, and this view is generally accepted. The "beta" carbon atom is the second from the end of the chain, and thus the catabolism is understood to consist essentially of a progressive cleavage of two carbon atoms at a time from the end of the long chain. At all events, in the only condition known in which this process of cleavage is arrested, i.e., in ketosis, the arrest occurs at the four carbon atom stage, a fact which coincides with such a theory. The four carbon fatty acid, butyric acid, has the formula



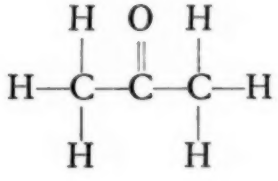
and it undergoes oxidation at the "beta" carbon atom to form beta-hydroxybutyric acid:



On further oxidation beta-oxybutyric acid yields acetoacetic acid,



and acetone,



These substances, with the single exception of acetone, are not regarded as abnormal products of fat metabolism, but on the contrary are considered as forming a part of the normally unbroken series of oxidation products of which the last are carbon dioxide and water.

The essential abnormality in metabolism in the condition of ketosis, therefore, is not the formation of the ketone bodies as such, but rather the failure of these latter substances to undergo still further oxidation to CO_2 and H_2O according to the normal sequence.

It is interesting to note in this connection that in patients in whom, due to lack of normal secretion from the islands of Langerhans (diabetics), the sugar metabolism is markedly disturbed, and consequently the fatty acid catabolism characteristically shows the arrest under discussion, the feeding of fats containing an odd number of carbon atoms even in large amounts fails to produce a condition of ketosis. The reason appears to be that since cleavage occurs at the beta-carbon atom there never does occur a four carbon atom stage in the catabolism and consequently no formation of ketone bodies.

Van Slyke and Fitz[5] have been able to show that the total amount of acetone bodies (calculated as acetone) circulating in normal blood is 1.3 to 2.6 mg. per 100 c.c. of blood, whereas in the blood of patients exhibiting ketonuria 10–40 mg. (even as much as 350 mg.) are frequently found. Inasmuch as acetone is a very diffusible substance it is rapidly excreted by the kidney, and, accordingly, the concentration of this substance in the urine is much greater than that in the blood at any given time.

As previously stated, it has long been a fact of common clinical knowledge that the appearance of ketosis is associated with disturbances of sugar metabolism. The measurement of this relationship has been made possible, however, only as the result of the fairly recent development of accurate methods of chemical blood analysis. Such methods have revealed that whenever sugar metabolism reaches a certain low ebb, as shown usually by a marked increase in the concentration of the

sugar in the blood, the catabolism of fats develops the characteristic arrest at the four carbon atom stage, and ketosis rapidly ensues.

The most obvious explanation for this phenomenon is that some product of sugar metabolism must be present to unite with the products of fat metabolism before the latter can pass the four carbon atom stage. This substance was supposed by Geelmuyden[6] to be glycuronic acid, but his hypothesis has been rendered highly improbable by the discovery that other substances beside fats can form ketone bodies and that other substances beside glucose are capable of yielding substances possessing the property of assisting in the complete metabolism of such ketone bodies.

It has been shown that certain of the amino-acids derived from proteins, the "alpha amino-acids," leucine, trypsin, and phenylalanine, are capable of forming a small quotum of ketone bodies. These acids, when fed to diabetics or added to the blood of experimental animals in perfusion experiments, are found to be capable of producing ketones.

Conversely, glycerol has been found capable of yielding products which assist in the complete oxidation of the fatty acids.

A comprehensive term is, therefore, needed to describe that class of bodies which are capable of uniting with the four carbon atom products of fat and protein metabolism in order that further and complete catabolism may take place, and such substances have been called "antiketogenic bodies"; another term is needed to describe the substances capable of producing ketone bodies, and these have been called "ketogenic substances."

In using this terminology it is evident that at least one molecule of antiketogenic substance must be present for every molecule of ketogenic substance metabolized in order that ketosis may not result. Actually, the relation between ketogenic and antiketogenic substances in the diet and the control of the ketogenic-antiketogenic ratio is a very complex affair

for the reason that the proteins, carbohydrates, and fats of the body are capable of undergoing certain metamorphoses from one to the other and back again, and frequently the practical problems, particularly in the diabetic patient, are most involved.

The variety of acidosis known as ketosis is of especial importance in surgery and for that reason has been considered at some length. Occurring as it does in connection with starvation, pyrexia, ether and chloroform anesthesia, as well as with diabetes mellitus, the surgeon needs particularly to be conversant with its manner of production.

c. Alkalosis Resulting from a Decrease in Carbonic Acid: Any condition which is capable of producing hyperpnea is capable of producing alkalosis provided that the factors of circulation and pulmonary architecture remain constant; thus mild degrees of alkalosis may be induced by voluntary hyperventilation. The condition of involuntary hyperpnea, however, produces more marked and permanent alkalosis. Involuntary hyperpnea is most frequently due to stimulation of the respiratory center by pressure, inflammatory processes, pyrexia, or psychic factors such as are found in hysteria.

d. Alkalosis Resulting from Accumulation of Administered Alkali: The relative ease with which the normal acidity of the urine can be reduced or changed to a condition of actual alkalinity by the administration of alkalis by mouth has already been mentioned in another connection. The normal succus entericus of the intestine is alkaline, and relatively enormous amounts of this substance are absorbed daily under physiological conditions. The addition of considerable quantities of alkali to this normal burden is easily tolerated, and under these conditions a corresponding alkali burden is placed on the buffers of the blood stream at least temporarily or until the kidney can arrange to excrete the excess. This function of excretion the kidney is able to perform only slowly so that the temporary net result of massive alkali administrations is the production of alkalosis.

Since, furthermore, the readjustment of the alkali content of the blood stream depends primarily on the kidney, readjustments may be unusually slow in case the kidney is damaged. The development of akalosis as a result of accumulated alkali thus may represent fundamentally a condition of over-dosage on the one hand or diminished urinary secretion on the other.

Over-dosage of alkali becomes a very real danger whenever alkalis are administered parenterally. Not very many years ago the intravenous injection of sodium bicarbonate was much more widely practiced than at present in connection with the treatment of acidosis. The clinical measurement of degrees of acidosis was at that time a matter of difficulty, and not infrequently unduly large amounts of bicarbonate were unwittingly added to the blood stream, no accurate means of checking the requirements of the case being available. In many instances the end-result of such uncontrolled administration was the mere changing of a condition of alkalosis for one of acidosis, and frequently the recipient of the treatment was actually worse off in the end than in the beginning.

E. ALKALOSIS DUE TO REPLACEMENT OF OTHER IONS BY BICARBONATE IONS: Clinically by far the most important mechanism in the development of alkalosis is the replacement of the chlorine ion by the bicarbonate ion. As previously mentioned, the chlorine ion is more reactive than the bicarbonate ion and displaces it from its base-forming radicals to produce one variety of acidosis; but when, for one reason or another, the body loses its normal chlorine content this reaction becomes reversed, and as chlorine is withdrawn bicarbonate replaces it, with the production of alkalosis. Chlorine is lost to the body most rapidly and characteristically as the result of the persistent loss of hydrochloric acid from the stomach either by vomiting, repeated gastric lavage, or the formation of a gastric fistula. Persistent massive vomiting being particularly prone to occur in connection with obstruction to the upper intestinal tract, as in hypertrophic pyloric stenosis, carcinoma of the pylorus of the stomach, and duodenal ileus,

these conditions characteristically are apt to give rise to an early and acute variety of alkalosis. Postoperative vomiting is more apt to be severe and persistent in connection with operations on the biliary tract than in connection with most other operative procedures, and for this reason postoperative alkalosis tends to occur frequently in connection with biliary surgery.

VI. The Clinical Recognition of Acidosis and Alkalosis

Postoperative acidosis may occasionally be due to any of the factors previously mentioned in connection with the general discussion of the mechanisms concerned in the production of this condition, but certain factors combine to predispose patients postoperatively to the development of that particular variety of acidosis previously designated as ketosis.

In the preceding description of ketosis the rôle of starvation was especially emphasized. Surgical patients, for obvious reasons, characteristically undergo a variable period of starvation, and whenever this period is prolonged the danger of ketosis must be remembered. In estimating the probable hazard from this source the postoperative period of food denial must not alone be considered but also any preoperative restriction of diet which may have been suffered either voluntarily because of food intolerance or involuntarily because of therapeutic restrictions.

Previous to the general recognition of the dangers inherent in starvation, the preoperative preparation of patients frequently involved denial of food for many more hours just prior to operation than is now considered either desirable or safe. In this connection it must be especially remembered that growing children develop starvation acidosis much more readily than adults, and undoubtedly many children have in times past been sacrificed on the altar of too rigorous preoperative preparation.

The especial susceptibility to starvation acidosis of diabetic patients has been mentioned at length in another connection.

It must, however, be remembered that the "potential diabetic," i.e., the patient with a low sugar tolerance, is subject to the same danger as the frankly diabetic patient though, of course, to a less degree. Such a dysfunction as diminished sugar tolerance because of its inherent nature is not likely to be detected by the ordinary preoperative maneuvers in vogue at present, and unless the medical attendant bears the condition specifically in mind in connection with all his patients, he may be occasionally at a loss to explain the condition of the exceptional patient who develops a degree of acidosis apparently unwarranted by circumstances.

In the use of the "Ochsner treatment" for peritonitis and similar therapeutic procedures involving periods of relative or complete starvation, care must be taken that the patient be not saved from his organic disease only to be destroyed by the metabolic upset of acidosis.

General anesthesia also, even apart from attendant starvation, has for some time been appreciated as a source of danger in the production of ketosis. The exact mechanism involved is not thoroughly understood, but, as is well known, most or all of the agents used in the production of general anesthesia, but especially chloroform and ether, are excellent fat solvents. Bloor[7] has shown that this fat solvent action manifests itself in a very definite increase in the fat content of the blood stream during prolonged anesthesia. Presumably, the natural fat reservoirs of the body are partly saturated by the anesthetic agent during anesthesia, and the fat therein contained becoming more liquid and no longer subject to normal restraint, finds its way into the circulation. Fat, thus freed, apparently shows a tendency to undergo much more rapid metabolism than does stored fat, and unless adequate sugar metabolism occurs concomitantly with the fat mobilization, a greater or less degree of acidosis invariably develops.

A somewhat more complicated variety of acidosis is that type which is frequently encountered in the severe diarrheas, especially in the infantile diarrheas. As an illustration of the

manner in which various mechanisms may interact to favor the development of acidosis a slight expansion of the subject of the acidosis of severe diarrhea may be useful. Diarrhea results, of course, from inflammation of the intestinal mucosa, whatever its etiology. In infants diarrhea is apt to be due to some form of intestinal infection, but may be secondary to parenteral infection such as mastoiditis; in adults infection, infestation, or local chemical irritation may be responsible.

As a result of intestinal inflammation exudates are formed, and these add to the normal bulk of the intestinal contents and thus tend to produce undue elimination, but the fundamental pathology is a functional disturbance of the *absorptive* mechanism whereby the intestinal contents tend to be passed on, to, and through the rectum unchanged. The net result of diarrhea is accordingly the immediate loss of large quantities of intestinal secretions rich in bicarbonates.

Although this mechanism of bicarbonate loss undoubtedly accounts for much of the acidosis, many factors contribute secondarily. These latter are associated, for the most part, with the dehydration which almost inevitably ensues when large quantities of fluids are lost to the body, and are directly dependent upon blood concentration.

The immediate effect of blood concentration is, of course, circulatory embarrassment; the viscosity of the blood becomes so great that capillary stasis occurs. Capillary stasis produces the condition of anoxemia which results partly from interference with local internal respiration and partly from interference with external respiration through deficient pulmonary circulation. Thus in diarrhea the primary acidosis of base bicarbonate deficiency is reinforced by the acidosis of carbon dioxide retention.

Incidental to blood concentration and anoxemia still other mechanisms tending to produce increased acidosis are favored. Perhaps the least important of these is increased lactic acid production. Lactic acid is produced during muscular contraction, and although lactic acid is a weak acid the lactate ion is

sufficiently reactive to displace bicarbonate ions from their associated base forming radicals. The excessive muscular efforts of the diaphragm and accessory muscles of respiration incident upon an already established anoxemia tend to form excessive amounts of lactic acid, which in turn tend to neutralize additional base bicarbonate and to establish a vicious circle, decrease of base bicarbonate due to loss by way of the intestinal tract leading to a condition of anoxemia, and anoxemia in turn leading to excessive lactic acid production and further diminution of base bicarbonates.

Furthermore, in a generalized anoxemia such as that under discussion all of the functions of the parenchymatous organs suffer to a greater or less extent. The kidney parenchyma constitutes no exception to the rule and, as previously emphasized, the kidney performs a very important function in maintaining the acid-base balance under normal conditions by eliminating certain acid forming substances in the urine. The particular substances concerned are mainly the acid phosphates and the sulphates. Acid phosphate and sulphate ions, like lactate ions, are capable of displacing bicarbonate ions from their base forming radicals, and thus anoxemia in its action on urinary secretion is seen to favor the establishment of more and more severe grades of associated acidosis.

The treatment of the acidosis of severe diarrhea, as can readily be appreciated from these considerations, is not, therefore, an entirely simple matter. It may be attacked from four different points of view:

1. An attempt may be made to replace base bicarbonate loss by base bicarbonate administration.

2. Blood concentration may be rectified by the copious administration of fluids. Since fluid cannot be absorbed sufficiently well by the gastrointestinal tract it must naturally be introduced parenterally.

3. Diuresis may be favored in an attempt to rid the body of retained acid forming radicals.

4. Rectification of the fundamental pathology may be attempted by seeking to discover and eradicate the factors initially responsible for the diarrhea.

To mention in detail the possible rôle in the production of acidosis of (1) dehydration, (2) of limitation of respiration, as by too tight bandaging and by operative incision, (3) of embarrassment of circulation, as by loss of blood, (4) of kidney damage, and of the host of other contributory factors that may be responsible for postoperative acidosis in general would be but to recapitulate the entire discussion of the subject that has gone before. It should be emphasized, however, that not enough attention has been paid in the past to the very close association between hemorrhage and acidosis. Blood transfusion especially tends to correct acidosis by restoring to the blood stream its normal quotum of carbon dioxide carriers, viz., the erythrocytes, and thus attacks the condition at its source.

The recognition of acidosis clinically in the preoperative or postoperative patient is oftentimes no less difficult than is the understanding of the mechanism by which the condition is produced. Usually acidosis cannot be diagnosed outright, but should be suspected whenever a mental analysis of the case seems to indicate this as the possible cause of symptoms and signs like the following:

1. Drowsiness or mental sluggishness
2. Irritability
3. Hyperpnea
4. Nausea and vomiting
5. Headache
6. Abdominal pain
7. Dehydration
8. Partial suppression of urine
9. Cyanotic or cherry red lips
10. Convulsions
11. Coma

As will be readily understood, none of these symptoms and signs are pathognomonic. They may all at times represent conditions fundamentally quite unrelated to the one under discussion, and to diagnose acidosis on the basis of one or a combination of such symptoms and signs in the absence of laboratory investigations would be hazardous. The determination of the carbon dioxide combining power of the plasma by the method of Van Slyke is a relatively simple laboratory procedure and is one which places at the disposal of the clinician reliable information as to the actual acid-base balance of his patient. Whenever the condition of the patient becomes dubious and a state of acid-base imbalance could account for that condition, no delay should be countenanced in applying the necessary test to solve the dilemma.

The presence of ketone bodies in the urine, though often associated with acidosis, is not necessarily so associated. Ketonuria is occasionally encountered in connection with a normal acid-base balance or even in actual alkalosis.

Postoperative alkalosis has been recognized as a possible surgical complication only within recent years. The occurrence of alkalosis in connection with the vomiting of high intestinal obstruction has been emphasized by a number of investigators, and during the course of the examination of the mechanism by which such alkalosis is produced, evidence has accumulated to show that continuous vomiting, however produced, tends to increase the carbon dioxide combining capacity of the blood. The sequence of events in the establishment of such alkalosis seems to be relatively simple. Gastric secretion tends to be rather strongly acid because of its hydrochloric acid content. Normally this acid is not lost to the body because it is passed on into the duodenum, is neutralized by the alkaline succus entericus of the small intestine, and is subsequently absorbed, not as free acid, to be sure, but as the neutralization products of free acid. In this way no acid forming radicals are permanently lost. If, however, the acid contents of the stomach be expelled by vomiting, the body is thereby deprived of a

considerable amount of free acid. The chlorine ion of the expelled hydrochloric acid is an acid radical, i.e., it is capable of displacing the bicarbonate radical of base bicarbonate, and when this radical is removed the process is reversed, a corresponding amount of base bicarbonate is immediately formed, and the base bicarbonate content of the blood stream is correspondingly increased.

The alkalosis of excessive vomiting tends to be maximal, accordingly, when (1) the amount of vomited material is maximal, and (2) when gastric acidity is high. These two conditions tend perhaps most frequently to be fulfilled postoperatively following operations on the biliary tract and in connection with the development of gastric dilatation. Occasionally ileus develops as a postoperative complication, and in such an event alkalosis may be expected to ensue. The free use of the indwelling stomach tube and the method of continuous duodenal lavage are not without danger, since much gastric juice may be drained away in the use of such methods.

Because during excessive vomiting large quantities of water are characteristically expelled from the body, dehydration tends to occur as an accompaniment of developing alkalosis.

The symptoms and signs of incipient alkalosis are perhaps even more indefinite than those of acidosis; no one symptom or sign is pathognomonic, nor is any combination of symptoms and signs. The condition may be suspected in the presence of:

1. Dehydration.
2. Blood concentration, increase of red cells and hemoglobin.
3. Emesis of large amounts of watery bile-stained material.
4. Low blood-pressure.
5. Marked asthenia.
6. Increase of blood non-protein nitrogen, urea, and creatinine.
7. Presence of urinary albumin and casts.

Clinically, as will now be appreciated, the symptoms of postoperative acidosis and alkalosis are similar; there is usually

a prolongation of the period of immediate reaction from the effect of the operation, vomiting may be persistent, there may be periods of restlessness alternating with periods of languor together with a slight elevation of temperature and flushing of the skin. Headache is possibly more frequent in alkalosis. Acetone bodies may be present in the urine in both conditions. The differentiation depends primarily upon the laboratory determination of the carbon dioxide combining power of the plasma. When this combining power is found to be abnormally low or high, and acidosis or alkalosis can therefore be accurately diagnosed the treatment of the presenting condition, of course, immediately comes into question.

VII. The Treatment of Acidosis and Alkalosis

In an attempt to minimize the inherent difficulty of presenting an orderly discussion of the subject of acid-base balance the matter of treatment has already received considerable attention. For this reason the principal object of any specific discussion of treatment at this point is to summarize and unify what has already been said in a fragmentary way.

A. The Treatment of Acidosis: To state that the treatment of postoperative acidosis is primarily prophylactic is but to repeat an observation which has been applied to so many conditons that it is in danger of becoming hackneyed and unconvincing. In few conditions, however, is the importance of prophylaxis so great as in postoperative acidosis. The four most important factors in the prophylaxis are:

1. Reduction of preoperative starvation to a decided minimum
2. Preservation of water balance and scrupulous prevention of dehydration
3. Parenteral administration of dextrose in quantities sufficient to take care of energy requirements whenever adequate nourishment cannot be tolerated by mouth
4. Massive blood transfusion in cases in which blood loss is considerable.

No considerable expansion of this subject need be attempted at this point, because rather comprehensive references to each of these factors have been made in other connections. However, for the sake of emphasis the functions of both water and dextrose in the prevention of acidosis may be summarized briefly.

Water:

1. Tends to prevent the acidosis of blood concentration at its source, since because of its diluent action it makes possible a free capillary circulation in the parenchymatous organs and thus facilitates internal respiration.

2. Acts as the best available diuretic and thereby tends to promote acid excretion by the kidney.

3. Adds bulk to the circulation and thereby tends to prevent the acidosis of circulatory failure; this action is, of course, manifested in maintaining the normal interchange of gases in the pulmonary alveoli, i.e., the maintenance of adequate external respiration.

4. Tends, because of its high specific heat, to regulate the body temperature thus preventing unduly active catabolism of carbohydrates and the consequent production of ketosis.

Talbot, Shaw, and Moriarty[8] have shown that in the case of acidosis developing in children as the result of fasting few subjective symptoms are experienced so long as large amounts of water are ingested and excreted. When fluid intake is diminished the children complain of abdominal pain and become flushed and alternately anxious and languid.

Dextrose:

1. Supplies a readily available source of energy while at the same time sparing fat catabolism, and also preventing the production of ketosis by supplying antiketogenic bodies to neutralize the ketogenic bodies derived from unavoidable fat catabolism.

2. Acts as a diuretic second only in efficiency to water itself and thereby tends to prevent the retention of acid-waste products.

In the severest types of acidosis a direct attack may be launched on the carbonic-acid-base-bicarbonate ratio by the intravenous injection of sodium bicarbonate. When attempting such therapy it must be remembered, however, that a merely temporary expedient is being adopted and that the utmost

that can be expected is a temporary readjustment of values, such that the patient does not immediately die of increased hydrogen ion concentration. Bicarbonate therapy establishes no direct contact with the fundamental pathology, which, of course, represents excess formation of acid radicals, and unless this excess formation of acid radicals can be adequately prevented, the condition of the patient is permanently improved not at all.

Sodium Bicarbonate Solution for Intravenous Injection

A suitable solution of sodium bicarbonate for intravenous injection may be made by weighing out on a piece of sterile paper 5 gms. of sodium bicarbonate, removing the bicarbonate from the middle of a clean package of reliable manufacture. The transfer of the material to the sterile paper should be by means of a metal spatula previously sterilized by flaming. The sodium bicarbonate is then dissolved in 100 c.c. of sterile freshly distilled water. Such a solution is neither isotonic nor absolutely sterile, but may be given intravenously with relatively little danger.

In infants and children, however, in whom the subcutaneous or intraperitoneal administration of the drug is deemed advisable, such a solution is unsuitable because of its lack of sterility and because also of its lack of isotonicity. Inasmuch, furthermore, as solutions of sodium bicarbonate can not be sterilized by heating because they decompose into the irritating substance sodium carbonate, sterilization of such solution can be accomplished only by means of filtration through a Berkefeld filter. To make a suitable solution, therefore, for either subcutaneous or intraperitoneal injection, it is necessary to adopt the following procedure: Dissolve 1.5 gms. of sodium bicarbonate in freshly distilled water. Add sufficient phenol red to the solution to produce a distinct coloration. Pass solution thus made through a Berkefeld filter and just prior to use allow carbon dioxide gas to bubble through the solution under sterile conditions until the color of the solution changes

from red to orange. A dose of sodium bicarbonate which is usually safe consists of 0.5 gms. of sodium bicarbonate per kilo of body weight. It is roughly equivalent to one-fourth of the sodium bicarbonate normally found in the body fluids of a patient.

The Administration of Sodium Bicarbonate and the Development of Tetany: The danger of the development of tetany in connection with the administration of sodium bicarbonate has been appreciated for a number of years. Numerous cases of tetany developing in children under such therapy have been reported[9] and alkali tetany in adults is by no means unknown.[10] The mechanism involved in the development of this complication is open to question.

According to Van Slyke[11] and his followers tetany may be expected to develop whenever the pH of the plasma reaches a value of about 7.8, regardless of the manner in which this change is effected. On the other hand, Greenwald[12] and his followers contend that alkalosis as such plays an unimportant part in the development of sodium bicarbonate tetany, and that the tetany of this form of alkalosis represents essentially a condition of sodium poisoning. According to the latter conception the appearance of tetany is an indication of the poisonous effect of the sodium ion.

Denis and von Meysenbug[13] have presented evidence to substantiate Van Slyke's hypothesis with respect to the action of sodium bicarbonate as such, but have also apparently demonstrated that the sodium ion itself is capable of producing a generally similar condition of spasmophilia in the absence of increases of pH or CO^3 content. Such spasmophilia was found to occur following the injection of large amounts of sodium chloride or sodium sulphate.

B. TREATMENT OF ALKALOSIS: Since varying degrees of dehydration characteristically accompany the development of alkalosis, the administration of quantities of water is invariably indicated. The stomach and upper intestinal tract being intolerant to nourishment of all kinds, parenteral administration

of fluids becomes necessary. A metabolic upset like the one under discussion is invariably a matter of grave concern, so that temporization with relatively uncertain methods of fluid administration cannot be trusted. Intravenous infusion is usually the method of choice.

Since, furthermore, alkalosis usually depends partly upon a chlorine ion deficit an attempt should be coincidentally made to supply an excess of chlorine ions. In connection with the use of intravenous infusion this may conveniently be attempted by using a hypertonic solution of sodium chloride as the infusion vehicle. Sodium chloride solutions of a strength between 2 and 5 per cent are suitable, but in view on the one hand of the large amounts of fluid required, and on the other, of the danger of pushing the administration of markedly hypertonic solutions too vigorously less concentrated solutions, 1 per cent or 2 per cent and in larger amounts are much to be preferred.

When alkalosis is dangerously high an attempt may be made to supply chlorine ions in a still more available form; ammonium chloride when given by rectum is a very satisfactory substance, as it is absorbed relatively rapidly. Calcium chloride can be used intravenously and serves as an easily available source of chlorine ions.

The intravenous injection of sodium acid phosphate may be used as a last resort. This substance is an acid salt normally found in the blood stream and excreted by the kidney. The rationale of its use in alkalosis depends upon its acid properties, and the use of this substance makes a direct attack on the acid-base balance of the blood much in the same manner as does the use of sodium bicarbonate in the treatment of acidosis. The administration of this substance also, like the administration of sodium bicarbonate, is not without danger, because it is impossible to tell by observation of symptoms and signs the extent of the acid-base readjustment. The danger of exchanging an acidosis for an alkalosis is great, unless repeated CO_2 determinations are made at frequent intervals. Further-

more, the exhibition of this substance may be expected at best to give only symptomatic relief, since neither the dehydration nor the hypochloremia which usually underlies the condition is alleviated in the slightest. The elimination of this substance by the kidney is relatively rapid under normal conditions of renal activity, and consequently the effect of sodium acid phosphate therapy may be expected to be somewhat transitory.

Hartmann's "Combined Solution" of "Buffer Salts"

From the point of view of the therapy of acidosis and alkalosis, an ideal situation would be one in which there could be administered a single solution of such composition as to correct a condition of acidosis on the one hand or a condition of alkalosis on the other. From the discussion that has preceded it will be readily seen that such a solution must needs be capable of performing the four following functions: (1) It must contain a sufficient amount of water to combat the dehydration which is almost invariably present in both acidosis and alkalosis. (2) It must contain sufficient chloride, preferably in the form of sodium chloride, to conteract the chloride deficiency which is characteristic of cases of alkalosis. (3) It must be capable of releasing sufficient base-bicarbonate to neutralize any excess concentration of hydrogen ions which may be present in acidosis, and (4) it must contain some chemical mechanism which will prevent intoxication by the sodium ion of the sodium chloride such as might occur in cases of acidosis in which no excess of sodium ion is required. Such a solution has actually been devised by Hartmann for use clinically. Theoretically the solution seems to fulfil adequately all of the above named requirements, and although the exact clinical evaluation of this solution has not yet been subjected to the acid test of sufficiently wide usage at the present writing, either the solution in its present form or the solution as it may subsequently be modified seems to promise much for the future.

The solution is made as follows: Into a 1-liter volumetric flask measure 60 c.c. of C. P. lactic acid, add enough dry phenol red indicator to color the solution preceptibly. Neutralize the solution with a saturated solution of sodium hydroxide from which the carbonate has been previously removed by sedimentation. Add 150 gms. of sodium chloride, 10 gms. of calcium chloride, and 5 gms. of calcium chloride crystals (i.e., calcium chloride which contains two molecules of water of crystalization). Add sufficient freshly distilled water to make exactly 1 liter. Transfer the solution without losing any of it to a clean beaker and boil the solution for thirty minutes in order to hydrolize the lactic acid anhydride resulting from the chemical action which takes place when the preceding reagents are brought together. During this process of boiling neutralize the solution with strong sodium hydroxide as frequently as the color of the solution indicates that it is becoming acid. At the end of thirty minutes cool the solution to room temperature, replace it in the volumetric flask, and restore the original volume with distilled water. Filter the solution through fine mesh filter paper. Divide it into convenient amounts, place it in suitable receptacles and autoclave it at 15 lbs. pressure for thirty minutes. Each 10 c.c. portion of the solution contains 85 per cent lactic acid (as sodium lactate) 0.6 c.c., sodium chloride 1.5 gms., potassium chloride 0.1 gm., calcium chloride 0.05 gm. The hydrogen ion concentration ranges between 7.3 and 8.7. *The solution is diluted with 25 times its volume of sterile freshly distilled water before injection.*

It is usually injected intravenously in adults but may be administered subcutaneously or intraperitoneally in infants and young children or in other patients in whom intravenous administration is for one or another reason undesirable or contraindicated. Instead of distilled water sterile dextrose solution of any proper percentage may be used as a diluent. The dextrose solution may be preferable especially in those cases in which it is desirable to provide the patient with readily available food energy, in those cases in which there

has been damage to the liver, or in those cases in which the diuretic action of the dextrose is desired.

Because of the relatively large amount of water this solution contains it has a tendency to restore diminished blood volume and to promote diuresis. The chloride ion is supplied in relatively large amounts as sodium chloride. Thus an excess of chloride ions is available if needed. The solution contains potassium and calcium ions, however, in sufficient amounts to balance the excess of chloride ions in those cases in which the latter are not needed. Because of the sodium lactate present in the solution, it is a potential alkalinizer, that is the solution of sodium lactate gradually decomposes to form sodium bicarbonate. This reaction, however, does not occur at a rate so rapid that it exceeds the excretory ability of the kidney and therefore does not accumulate in extensive amounts in the blood stream, being either excreted as formed on the one hand, or being utilized for the correction of acidosis on the other.

VIII. RÉSUMÉ

According to modern physical chemistry acids may be defined as substances which dissociate in watery solution in such a way as to form hydrogen ions, and bases as substances which dissociate to form hydroxyl ions. The measure of the acidity of a substance is its ability in solution to produce a greater or lesser number of hydrogen ions, whereas similarly the measure of its basicity is its ability to produce hydroxyl ions. Since, however, water itself is capable of dissociating into both hydrogen and hydroxide ions and does so dissociate, there is in every watery solution a mixture of both hydrogen and hydroxyl ions regardless of whether or not there exist dissolved in it other substances which dissociate to form such ions. The fact that distilled, or pure, water is neutral in reaction does not mean that neither hydrogen nor hydroxyl ions are present but rather that precisely as many hydrogen ions are present as hydroxyl ions.

When acids are added there results simply an increase of the hydrogen ions over the hydroxyl ions, there still being a certain number of hydroxyl ions due to the dissociation of water itself; similarly when bases are added the hydroxyl ions outnumber the hydrogen ions, though a certain number of the latter are still present, due again to the dissociation of water.

The addition of an acid or a base to a watery solution does not, however, simply add a certain number of hydrogen or hydroxyl ions to the solution, as the case may be, but brings about a reciprocal change in the hydrogen-hydroxyl ion ratio, i.e., the addition of hydrogen ions *ipso facto* decreases the number of hydroxyl ions previously present, and vice versa. This phenomenon accounts for the fact that whereas the addition of an acid to a watery solution always changes the latter in the direction of increased acidity or decreased alkalinity, as the case may be, the preexisting composition of the solution as well as the amount and strength of the added acid or base determine the exact amount of the change.

The composition of human blood is such, due to the presence in it of various salts and proteins in solution, that the addition of comparatively large quantities of hydrogen ions as acids or of hydroxyl ions as bases change its hydrogen ion or hydroxyl ion concentration but little or not at all, i.e., due to reciprocal changes between the added acid or alkali and the substances already present in solution, the net difference between the hydrogen and hydroxyl ions present afterward is not different from its previous value.

The addition of acid or basic radicals does, however, affect the buffer substances, and the net result is a diminution in the ability of the buffer substances to withstand the further addition of more of the acid or basic radicals even though the actual hydrogen ion concentration of the blood may not be affected in the least. Assaults upon the normal buffer mechanism, the hydrogen ion concentration itself being unaffected, constitute "compensated" acidosis or alkalosis. On the other hand, when the normal buffer mechanism breaks down and

actual changes in hydrogen ion concentration occur the conditon is known as a "decompensated" acidosis or alkalosis.

A. Neither acidosis nor alkalosis can be diagnosed merely on the basis of clinical manifestations.

(1) Common clinical findings in acidosis include:
   a. Irritability or drowsiness and mental sluggishness
   b. Nausea and vomiting
   c. Dehydration, blood concentration
   d. Cyanosis or "cherry red" lips
   e. Partial suppression of urine
   f. Headache
   g. Convulsions and coma

(2) Common clinical findings in alkalosis include:
   a. Asthenia
   b. Vomiting of watery, bile-stained material
   c. Dehydration, blood concentration
   d. Low blood pressure
   e. Urinary albumin and casts
   f. Headache
   g. Tetany and coma

Disturbances in acid-base balance should be considered in all postoperative cases in which convalescence is unsatisfactory and findings like those mentioned, when present, cannot be adequately explained on some more obvious basis.

B. The most useful short method of determining the acid-base balance is Van Slyke's blood-gas determination, the "carbon-dioxide-combining-power of the plasma."

(1) It is a value obtained by measuring the amount of carbon dioxide liberated by the complete disintegration of the base bicarbonates.

(2) It is, therefore, simply an indirect way of measuring the concentration of the base bicarbonates themselves, a procedure which would be technically too difficult and too unreliable for routine use.

(3) The normal variation of the plasma CO_2 combining power is considerable, 53 to 77 volumes per cent. (By "volumes

per cent" is meant simply "volumes of CO_2 per 100 c.c. of plasma.")

(4) Values greater than 77 may be taken as indicating alkalosis, a greater-than-normal amount of base bicarbonate; values less than 53 may be taken as indicating acidosis, a less-than-normal concentration of base bicarbonate.

C. "In vivo" the ratio between the base bicarbonates ($BHCO_3$) and the carbonic acid (H_2CO_3) of the blood stream is the fundamental relation governing acid base balance,

$$\frac{BHCO_3}{H_2CO_3}$$

(This is but another way of saying that the base bicarbonates constitute the first line of buffer defense.)

(1) The addition of moderate amounts of acids to the blood stream changes the ratio in the direction of diminution of the base bicarbonates, but if compensatory elimination of carbonic acid occurs the ratio may immediately readjust itself (compensated acidosis).

(2) The addition of moderate amounts of bases to the blood stream changes the ratio in the direction of increase of the base bicarbonates, but, again, if compensatory retention of carbonic acid occurs the ratio may immediately readjust itself (compensated alkalosis).

(3) It should be sufficiently evident, however, that in spite of this compensation the amount of base bicarbonate undergoes in either case an absolute change, the measure of which is the "carbon dioxide combining power."

(4) Only when the ratio fails to readjust itself does an actual change in the hydrogen ion concentration of the blood occur (uncompensated acidosis or alkalosis).

D. The fundamental regulating mechanism of the carbonic acid in the blood is respiration: carbon dioxide in the blood is in equilibrium with carbonic acid in accordance with the simple formula:

$$CO_2 + H_2O \rightleftarrows H_2CO_3$$

It follows:

(1) That the integrity of the respiratory system must be maintained if changes in acid-base balance are to be prevented.

(2) That inasmuch as the integrity of the respiratory system is directly dependent upon integrity of the circulatory system, failure of the circulatory system affects the acid-base balance almost as directly as failure of the respiratory system itself.

(3) That inasmuch as the integrity of the circulatory system depends not only upon a sufficient volume of circulating fluid but more especially upon a sufficient number of circulating erythrocytes, blood transfusion often serves as an admirable means of combating acidosis almost at its source.

E. A secondary regulating mechanism of acid-base balance is the kidney. This organ when functioning properly:

(1) Excretes bases (particularly in the form of base bicarbonates) or

(2) Excretes acids (particularly in the form of acid phosphates),

when these substances are present in the blood stream in excessive amounts.

Practically and therapeutically it should be remembered

(1) that water is the most efficient diuretic and

(2) that, next to water, dextrose solution is the most efficient diuretic.

F. The fundamental chemical reactions responsible for the development of clinical acidosis and alkalosis may be tabulated as follows:

Acidosis results from:

(1) Increase in carbonic acid due to
   a. respiratory embarrassment
   b. circulatory embarrassment

(2) Decrease in base bicarbonates due to
   a. excessive elimination by the
      —alimentary tract
      —kidney

b. replacement of the bicarbonate ion with some more reactive ion
—lactate ion
—chlorine ion
—acid phosphate and sulphate ions
—diacetate and beta-oxybutyrate ions

Alkalosis results from:

(1) Decrease in carbonic acid (hyperventilation) due to
a. voluntary hyperpnea
b. involuntary hyperpnea

(2) Accumulation of administered alkali due to
a. faulty elimination
b. overdosage

(3) Replacement of other ions by the bicarbonate ion, especially the
a. chlorine ion
b. lactate ion

G. Attempts at readjustment of perverted acid-base balance by the addition of acids or bases directly to the blood stream are intrinsically irrational:

(1) Such methods are dangerous because unless controlled with the utmost care they may merely substitute an acidosis for an alkalosis, or vice versa.

2. They serve merely as temporary expedients because the added substances tend to be speedily removed from the circulation (mainly by diuresis).

(3) The acids or bases commonly used for the purpose may effect a readjustment of acid-base balance, but do not correct the fundamental abnormality.

The common substances used are sodium bicarbonate (in the treatment of acidosis), and sodium acid phosphate (in the treatment of alkalosis).

(1) Even though CO_2 determinations show the plasma bicarbonates to be at a low level the administration of sodium bicarbonate does not necessarily correct the abnormality, because not the plasma bicarbonates, but the red blood cell

bicarbonates are mainly concerned in the transportation and elimination of CO_2.

(2) In ketosis there is no fundamental deficiency of bicarbonates, but rather an excess of foreign acids; prevention of the formation of these acids can readily be accomplished.

(3) Sodium acid phosphate injections in alkalosis supply no chlorine ions to the circulation and therefore do not attack the abnormality fundamentally at all.

H. Unless some abnormality of pancreatic secretion exists (diabetes or possibly pancreatitis) the use of insulin to "buffer" dextrose solution for intravenous injection is irrational and sometimes distinctly dangerous.

(1) Insulin and dextrose do not react like two chemical compounds to form a new compound.

(2) One unit of insulin ensures the metabolism of 1 gm. of dextrose only in the completely depancreatized animal.

(3) The possible functions of insulin are:

a. It facilitates glycogen storage in the liver.
b. It possibly converts dextrose into some more oxidizable hexose.
c. It produces blood concentration by increasing the affinity of the tissues for water.

The rational treatment of acidosis and alkalosis depends upon an adequate understanding of the physico-chemical mechanisms responsible for acid-base imbalance. The problem is fundamentally one of prophylaxis. The active treatment in the already developed condition of acid-base instability should be directed against the cause.

The indications for accessory therapy are most commonly met by the administration of one or a combination of the following:

In acidosis:

1. Blood transfusion.
2. Intravenous infusion of glucose solution (without or without insulin).
3. Intravenous infusions of "artificial serum" solutions.
4. Intravenous infusion of sodium bicarbonate solutions (only rarely and in desperate cases).

In alkalosis:

1. Intravenous infusion of artificial serum solutions.

2. Intravenous infusion of sodium or calcium chloride solutions (either isotonic or slightly hypertonic).

3. Enteric administration of chlorides (especially ammonium chloride by rectum).

4. Intravenous infusion of acid sodium phosphate solutions of about 2 per cent strength (only rarely and in desperate cases).

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